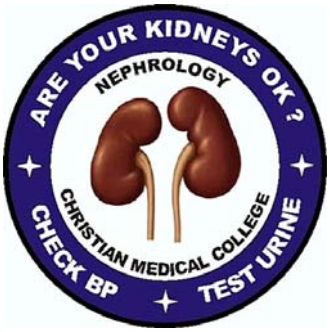
SPECTRUM OF BIOPSY PROVEN RENAL DISEASES IN THE PAEDIATRIC AGE GROUP BETWEEN 1997 – 2006 FROM A TERTIARY CENTER OF INDIA

A dissertation submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of the University regulations for the award of D.M. (Branch – III) (Nephrology).



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BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled "**SPECTRUM OF BIOPSY PROVEN RENAL DISEASES IN THE PAEDIATRIC AGE GROUP BETWEEN 1997 -2006 FROM A TERTIARY CENTER OF INDIA"** done towards fulfillment of the requirements of the **Tamil Nadu Dr. M.G.R. Medical University, Chennai for the D.M. (Branch–III) (Nephrology)** exams to be conducted in July 2009, is a bonafide work of the candidate **Dr.Anjali Mohapatra,** Senior Post graduate student in the Department of Nephrology, Christian Medical College, Vellore under my guidance and supervision. This dissertation has not been submitted, fully or in part to any other board or University.

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Acknowledgement

I thank God Almighty for making me able and providing me with right opportunities and right people at the right time. This dissertation would not have been possible without the support, encouragement, timely help and advice from many people.

I am greatly indebted to **Dr. George T. John,** Professor and Head, Department of Nephrology, Christian Medical College, Vellore for being instrumental in initiating this research venture, for his valuable inputs into the topic, and guidance through the ups and downs of the study.

My special thanks to **Prof. Dr. V. Tamilarasi** who deliberately extended her hearty co operation in preparation of this dissertation.

I owe a deep sense of gratitude to **Prof. Dr. Chakko K Jacob** for his encouragement in fulfilling the dissertation.

My sincere thanks to **Dr. Basu G** for his constant suggestion and insurmountable guidance throughout the study.

It gives me great pleasure to place on record my obligation to **Mr. V.M. Annapandian,** for his untiring interest and unstinted support generously given at every step of data analysis.

My special thanks to **Mr. Gowri Shankar** for his constant interest in preparing my thesis data.

I am very much grateful to all the office staff for their timely help and support.

I am obliged to my husband **Dr. Auro Viswabandya** who in spite of his busy schedule could squeeze time to be at my side for seeing the preparation of this dissertation through.

My heartful thanks to my son **Anweshi** for his patience and sacrifice towards the smooth completion of the dissertation.

I acknowledge the efforts of staffs of the Department of Pathology and Medical Records for making me able to collect the data for thesis.

I express my sincere gratitude to all the patients who were part of the study.

I would like to thank my colleagues for their help and support.

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Abstract

Background :

The incidence of renal diseases among paediatric age group is not uncommon and nephrotic syndrome is considered as the most common clinical and histopathological diagnosis among all types of renal diseases in children. However, there is a limited data on the distribution of various histopathological spectrum of biopsy proven renal diseases in the paediatric population from developing countries.

Patients and methods:

A retrospective as well as prospective study was performed from January 1997 to December 2006 at our center involving 1480 children (age 1 month to 18 years) who have undergone renal biopsy. The data was complete in 887 patients and this was analyzed.

Aim and objectives :

1. To study the distribution of various renal diseases in pediatric age group in our center
2. To analyze patient characteristics, clinical and biochemical parameters among each group of biopsy proven renal diseases.
3. To study the various modality of treatment and its out come among these patients.

Results:

The study included 887 children for whom biopsy reports were available. There were 554 males and 333 females. The distribution of various diseases were as follows: Minimal change disease in 303 (34.16%), Mesangial proliferative GN in 146 (16.45%), Lupus nephritis in 98(11.05%), Proliferative glomerulonephritis in 81(9.13%), IgA nephropathy in 61 (6.87%), Focal segmental glomerulosclerosis in 59(6.65%), Diffuse mesangial hypercellularity in

53(5.97%), Membranous glomerulonephropathy in 24(2.70%), Crescentic glomerulonephritis in 15(1.69%), Membrano proliferative glomerulonephritis in 8(0.9 %),Hemolytic uremic syndrome in 5 (0.56 %),Vasculitis in 3(0.33 %), acute interstitial nephritis in 3 (0.33 %),acute tubular necrosis in 2(0.22 %), granulomatous interstitial nephritis in 3(0.33%), end stage etiology of unknown etiology in 17(1.92 %) and inadequate sample in 2 (0.22%) children. Mean age at onset of MCD was 8.48 ± 4.7, 1-18 yrs years. In our patients, haematuria was seen in 9 % patients with MCD, 12.8 % patients with FSGS and 28.6% patients with MPGN. Hypertension was seen in 7% patients with MCD, 21.1%patients with FSGS and 12.1 % patients with MPGN.

Conclusion:

In children under 8 years of age, minimal change disease was the most common entity, whereas Focal segmental glomerulosclerosis predominated in children with age at onset greater than 8 years. The age at onset of nephrotic syndrome was significantly higher in the non-MCD group than the MCD group. The incidence of hypertension, microhematuria, gross hematuria and was significantly lower in the MCD group. MCD remains the most common histopathological subtype in Indian children with idiopathic nephrotic syndrome and the incidence of Membranoproliferative glomerulonephritis has been found to have declined. The incidence of lupus nephritis has increased. This study provides descriptive epidemiological biopsy data and highlights some important trends in changing prevalence of renal disease.

INTRODUCTION:

The diagnostic approach to the renal biopsy obtained from a child follows the same principles as it does for adult specimens, for example an assessment of adequacy and the presence of chronic changes, and a systematic evaluation of the glomerular, tubulointerstitial and vascular components, followed by the use of adjunctive investigations such as immunohistochemistry and electron microscopy. There can, however, be significant differences in the appropriate interpretation of the findings present as a consequence of both differences in the relative frequencies of specific pathological conditions and the effect of physiological age-related changes. The spectrum of paediatric renal disease encompasses the majority of entities seen in adult practice, although with a much lower incidence for many of these, in addition to a number of conditions either unique to or much more frequent in childhood. For this reason, although general renal biopsy processing or handling in the laboratory is identical irrespective of patient age, it is especially important to routinely process part of the biopsy for ultra structural examination in specimens from children as conditions such as Alport nephropathy and thin glomerular basement membrane (TGBM) disease can only be diagnosed by appropriate electron microscopic examination[1].

For some conditions, such as lupus nephritis, the role of the biopsy in childhood is identical to that in adult practice, namely to allow risk stratification and direct patient management, but the distribution of the histological patterns may be different from the adult population.

In other conditions, however, such as congenital nephrotic syndrome (CNS), biopsy is for primary diagnostic purposes, with the main differential diagnoses having no counterparts in adult practice.

REVIEW OF LITERATURE:

The routine evaluation of a percutaneous renal biopsy involves examination of the tissue under light microscopy, immunofluorescence (immunoperoxidase in some laboratories)[2] , and electron microscopy. Each component of the evaluation can provide important diagnostic information. The routine immunofluorescence examination of biopsy specimens should include (at a minimum) evaluation of IgG, IgM, IgA, C3, C1q, albumin, fibrin, and kappa and lambda immunoglobulin light chains.

Justification for the routine application of electron microscopy comes largely from studies in the 1960s and 1970s, which showed that this technique provided substantive diagnostic information beyond that obtained from light microscopy in nearly 50 percent of cases. However, most of these studies were performed at a time when immunofluorescence microscopy was not widely available.

To assess the present utility of electron microscopy, a study of 288 native renal biopsies performed over a six-month period in 1996 examined the diagnostic findings provided by light, immunofluorescence, and electron microscopy[3]. When viewed in combination with the results from light and immunofluorescence microscopy, electron microscopy provided:

- Required diagnostic information in 50 cases (21 percent)
- Important confirmatory data in 48 (21 percent)
- Additional unrelated findings in 8 (3 percent)

These findings are consistent with the results from earlier studies and support the continued use of routine electron microscopy. Diagnoses that commonly require electron microscopy included minimal change disease, focal and segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy, thin basement membrane disease and Alport

syndrome, postinfectious glomerulonephritis, HIV-associated nephropathy, amyloidosis, immunoglobulin deposition diseases, and fibrillary (immunotactoid) glomerulopathy.

INDICATIONS

The indications for performing a renal biopsy is determined in part by the presenting signs and symptoms[4,5]. The overall rate of native kidney renal biopsy (in number of procedures per million populations [pmp]) varies from over 250 pmp in Australia to less than 75 pmp in the USA[6] . The renal biopsy rate is higher in adults than in children.

These differences in renal biopsy rate are not driven by any differences in the spectrum of renal pathology, but rather by opinions regarding the value of the procedure in diagnosis, prognosis, and therapy. The results of the renal biopsy impact patient care in up to 60 percent of cases[7,8]. However, the utility of the biopsy may differ considerably based on the indication.

Isolated nonnephrotic proteinuria – A renal biopsy generally is not performed in a patient who presents with low-grade proteinuria (less than 500 to 1000 mg/day), absence of glomerular hematuria, usually normal renal function, and an absence of clinical or serologic evidence of a systemic disease that can cause glomerulonephritis (eg, systemic lupus erythematosus, vasculitis, or a paraproteinemia). Some of these patients will have mild primary focal glomerulosclerosis, IgA nephropathy, or membranous nephropathy[9]; however, immunosuppressive therapy would not be indicated in this setting, since the prognosis with nonnephrotic proteinuria is often excellent. Other patients will have secondary focal glomerulosclerosis as a response to ischemic injury (as in nephrosclerosis) or to nephron loss (as in reflux nephropathy).

EVALUATION OF PROTEINURIA IN CHILDREN

Introduction – Proteinuria as a marker of renal disease has been well established. The dilemma that faces the primary care physician is to differentiate the child with transient or other benign forms of proteinuria from the child with proteinuria from renal disease.

PATHOPHYSIOLOGY AND CLASSIFICATION

Normal protein excretion – Urinary protein excretion in the normal child is less than 100 mg/m^2 per day or a total of 150 mg per day. In neonates, normal urinary protein excretion is higher, up to 300 mg/m^2, because of reduced reabsorption of filtered proteins.

Approximately one-half of normal protein excretion consists of proteins secreted by tubular epithelium, mostly Tamm-Horsfall protein (uromodulin). The other half consists of plasma proteins including albumin, which accounts for approximately 40 percent of the total urinary protein, and low molecular weight proteins, such as beta-2 microglobulin and amino acids.

Abnormal protein excretion – Urinary protein excretion in excess of 100 mg/m^2 per day or 4 mg/m^2 per hour is considered abnormal in children. Nephrotic range proteinuria (heavy proteinuria) is defined as $\geq$ 1000 mg/m^2 per day or 40 mg/m^2 per hour.

There are three main mechanisms of increased protein excretion: glomerular, tubular, and overflow proteinuria.

Glomerular proteinuria – Glomerular proteinuria is due to increased filtration of macromolecules (particularly albumin) across the glomerular capillary wall. This may arise because of anatomical or functional lesions.

Glomerular proteinurias are a common cause of proteinuria in children. They may result from glomerular disease (most often minimal change disease) or from nonpathologic conditions such

as fever, intensive exercise, and orthostatic (or postural) proteinuria, in which protein excretion is increased only in the upright position.

Tubular proteinuria – Tubular proteinuria, which is less frequent, results from increased excretion of low molecular weight proteins such as beta-2-microglobulin, alpha-1-microglobulin, and retinol-binding protein. These molecules are normally filtered across the glomerulus and then largely reabsorbed in the proximal tubule. Interference with proximal tubular reabsorption, due to a variety of tubulointerstitial diseases, can lead to increased excretion of these smaller proteins.

Tubular proteinuria often is associated with other defects in proximal tubular function, including glycosuria, proximal renal tubular acidosis with bicarbonate wasting, and phosphaturia. In Fanconi's syndrome, all four of these proximal tubular defects occur.

Only albumin is detected by the urine dipstick, while tubular proteinuria is not detected by screening dipstick urinalysis.

Overflow proteinuria – Overflow proteinuria results from increased excretion of low molecular weight proteins due to marked overproduction of a particular protein to a level that exceeds tubular reabsorptive capacity. Overflow proteinuria is not observed in children; it is primarily observed in adults with a plasma cell dyscrasia (eg, multiple myeloma) who overproduce immunoglobulin light chains.

As with tubular proteinuria, overflow proteinuria with low molecular proteins will not be detected by screening dipstick urinalysis.

CAUSES OF PROTEINURIA IN CHILDREN

Glomerular proteinuria	
Primary Causes	**Secondary Causes**
Minimal change disease Congenital nephrotic syndrome "Finnish-type" Mesangial sclerosis Focal segmental glomerular sclerosis IgA nephropathy (Berger's disease) Membranoproliferative glomerulonephritis Membranous nephropathy Alport syndrome	Acute post-streptococcal glomerulonephritis Diabetes mellitus Systemic lupus erythematosus Henoch-Schönlein purpura

Tubular Proteinuria	
Primary Causes	**Secondary Causes**
Cystinosis Dent's syndrome Wilson's disease Lowe's syndrome Polycystic kidney disease Mitochondrial disorders	Heavy metal poisoning Acute tubular necrosis Tubulointerstitial nephritis Secondary to obstructive uropathy

Among children with persistent proteinuria, a complete history and physical examination is needed, including measurement of the blood pressure. Initial laboratory evaluation includes renal function tests (blood urea nitrogen and creatinine), serum electrolytes, cholesterol, albumin, and total protein. Other tests such as renal ultrasound, serum complement levels (C3 and C4), ANA, streptozyme testing, hepatitis B and C serology, and HIV testing should be considered if

appropriate. A voiding cystourethrogram should be considered if there is an abnormal ultrasound with scarring or a history of fever suggestive of urinary tract infections.

If this initial evaluation is normal, the urine dipstick should be repeated on at least two additional specimens. If these subsequent tests are negative for protein, the diagnosis is transient proteinuria.

If the proteinuria persists or if any of the studies are abnormal, the patient should be referred to a pediatric nephrologist. At this point, urinary protein excretion should be quantified by a timed collection, if obtainable.

Indications for renal biopsy – The role of renal biopsy in a child with isolated asymptomatic persistent proteinuria is controversial[10]. Many nephrologists recommend close monitoring for those children with urinary protein excretion below 500 mg/m^2 per day before considering a biopsy[1]. Monitoring should include assessment of blood pressure, protein excretion, and renal function. If any of these parameters shows evidence of progressive disease, a renal biopsy should be performed to establish a diagnosis.

There are limited data on the results of renal biopsy in such children.

In a retrospective review of 53 Japanese children with persistent isolated proteinuria, a significant glomerular disease was present in 25 (47 percent): 15 had focal segmental glomerulosclerosis (FSGS); four had IgA nephropathy, and three each had membranous nephropathy and diffuse mesangial proliferative glomerulonephritis without IgA deposition[11].

In a report of 461 Korean children with an abnormal urinalysis detected by school screening, only nine patients had isolated persistent proteinuria with protein excretion ≥2 g in a 24-hour collection[12]. Renal biopsy demonstrated changes consistent with minimal change nephrotic

syndrome in seven patients, and one case each of mesangial proliferative glomerulonephritis and membranous glomerulopathy.

Symptomatic child – Clinical manifestations in the symptomatic child with proteinuria may be general and nonspecific (eg, fever, malaise, weight loss), non-urinary specific (rash, purpura, arthritis), or urinary specific (eg, edema, hypertension, renal insufficiency). The underlying disorder may be primarily renal in origin or secondary to a systemic process. Diagnostic categories include infections, rheumatologic and immunologic disorders, and primary and secondary glomerular and interstitial diseases of the kidney.

- Children with heavy proteinuria and periorbital or peripheral edema must be evaluated promptly for nephrotic syndrome. The major manifestations of nephrotic syndrome are heavy proteinuria (protein excretion >1000 mg/m^2 per day or spot urine Pr/Cr ratio >1.0), edema, serum albumin <2.5 g/dL, and hypercholesterolemia. Almost all such children have idiopathic nephrotic syndrome, and management decisions should be made in consultation with a pediatric nephrologist.

Non-nephrotic children with persistent proteinuria who present with hypertension, an abnormal urinalysis, or an elevated plasma creatinine concentration should be referred to a pediatric nephrologist for further evaluation and possible renal biopsy.

- In patients with an abnormal ultrasound or history of febrile urinary tract infections, a voiding cystourethrogram should be considered if there is an abnormal ultrasound with scarring or a history of febrile urinary tract infections

Nephrotic syndrome – A renal biopsy typically is not indicated for the nephrotic syndrome in childhood.

In the absence of a systemic disease, it is quite likely that one of the three major causes of the idiopathic nephrotic syndrome is present: minimal change disease, focal glomerulosclerosis (accounting for over 80 percent of cases in adults and children) membranous nephropathy.

Renal biopsies in children under the age of six years with nephrotic syndrome may not be necessary, as over 90 percent will have minimal change disease. The necessity of renal biopsy for nephrotic syndrome in older children, adolescents, and adults has been controversial, but we now have a better appreciation of the different therapies in these disorders.

CLASSIFICATION : Children with nephrotic syndrome are classified based upon whether or not there are signs of systemic disease or of an active urine sediment.

- Primary nephrotic syndrome, which refers to nephrotic syndrome in the absence of an identifiable systemic disease. Within this category are patients with idiopathic nephrotic syndrome, who have bland sediment and no glomerular inflammation on renal biopsy and patients with primary glomerulonephritis, who have an active sediment and glomerular inflammation on renal biopsy.

- Secondary nephrotic syndrome, which refers to nephrotic syndrome in the presence of an identifiable systemic disease.

- Congenital and infantile nephrotic syndrome, which occur in children less than one year of age and can be either secondary (mostly due to infection) or primary. Two-thirds of nephrotic syndrome cases that occur during the first year of life and as many as 85 percent of cases that occur during the first three months of life can be explained by mutations in one of four genes[13].

Primary nephrotic syndrome – Primary nephrotic syndrome is defined as nephrotic syndrome in the absence of systemic disease. Within this category are two subgroups:

- Disorders associated with a bland urine sediment and lack of glomerular inflammation on renal biopsy. Included in this group are idiopathic nephrotic syndrome..
- Nephritic disorders associated with an active urine sediment (red cells and cellular casts) and the presence of glomerular inflammation on renal biopsy. Included in this group are membranoproliferative glomerulonephritis and IgA nephropathy, which are discussed separately.

Idiopathic nephrotic syndrome – Idiopathic nephrotic syndrome is the most common form of childhood nephrotic syndrome, representing more than 90 percent of cases before 10 years of age and 50 percent after 10 years of age[14]. Idiopathic nephrotic syndrome is defined by the association of the clinical features of nephrotic syndrome with renal biopsy findings of diffuse foot process effacement on electron microscopy and minimal changes (called minimal change disease [MCD]), primary focal segmental glomerulosclerosis (FSGS), or mesangial proliferation on light microscopy. It is unclear whether these three light microscopic patterns represent separate disorders or are a spectrum of a single disease process[15].

Most patients, particularly those who are young (<6 years of age), have histologic findings of MCD. The vast majority of patients with MCD (>90 percent) respond to glucocorticoid therapy[16]

MCD can be clinically differentiated from those with other causes of childhood nephrosis. This was illustrated in a classic study from the International Study of Kidney Disease in Children (ISKDC) of 521 children (age range, 12 weeks to 16 years of age) who presented with primary nephrotic syndrome. The study was conducted in 24 centers in North America, Europe, and Asia between 1967 and 1974[14]. Renal biopsies were obtained in all children.

Multivariate analysis demonstrated that clinical findings at presentation accurately differentiated children with MCD from those with other glomerular pathology[14]. These findings included:

- Age younger than 6 years of age
- Absence of hypertension
- Absence of hematuria by Addis count
- Normal complement levels
- Normal renal function

One exception to the age criterion is onset of nephrotic syndrome in the first year of life, particularly the first three months of life, which is much more likely to be due to a gene mutation and to be resistant to glucocorticoids[13].

Based upon these observations, an initial trial of glucocorticoid therapy is generally administered to children who are likely to have MCD based upon clinical diagnosis, thereby avoiding renal biopsy. Patients with idiopathic nephrotic syndrome are further classified based upon their response to empiric glucocorticoid therapy.

Glucocorticoid-responsive nephrotic syndrome – The majority of children with idiopathic nephrotic syndrome are glucocorticoid-responsive (also referred to as glucocorticoid-sensitive nephrotic syndrome). In these patients, the most likely histologic lesion is MCD, although some patients with FSGS will also respond to glucocorticoid therapy[15]. Patients who are glucocorticoid-responsive have a favorable long-term outcome.

- Glucocorticoid-resistant nephrotic syndrome – Approximately 25 percent of all children with nephrotic syndrome will not respond to glucocorticoid. The response rate is better in younger children, who are much more likely to have MCD. In an ISKDC study, only

about 10 percent of children less than 10 years of age failed to respond to glucocorticoids[16]. Patients with glucocorticoid resistant nephrotic syndrome have a worse prognosis than those who are glucocorticoid-responsive[16,17]. Some children with glucocorticoid-resistant nephrotic syndrome have genetic mutations of podocyte proteins.

Secondary nephrotic syndrome – Secondary nephrotic syndrome is defined as nephrotic syndrome associated with systemic diseases or is secondary to another process that cause glomerular injury. Within this category are the same two subgroups as in primary nephrotic syndrome:

- Disorders associated with a bland urine sediment and lack of glomerular inflammation on renal biopsy. Included in this group are some cases of membranous nephropathy (eg, due to lupus, penicillamine), secondary focal glomerulosclerosis due to nephron loss resulting from renal scarring or hypoplasia.

- Nephritic disorders associated with active urine sediment (red cells and cellular casts) and the presence of glomerular inflammation on renal biopsy. A variety of disorders are included in this group.

- Postinfectious glomerulonephritis and infective endocarditis.

- Systemic lupus erythematosus.

- Vasculitides such as Henoch-Schönlein purpura and rarely in Wegener's granulomatosis and microscopic polyangiitis.

- Other causes include sickle cell disease, which is usually associated with secondary focal glomerulosclerosis, Alport syndrome and hemolytic uremic syndrome.

ETIOLOGY – Minimal change disease (MCD) is the most commonly seen histopathology of childhood nephrosis. In the previously mentioned ISKDC study of 521 children who presented with nephrotic syndrome without systemic disease between 1967 and 1974, the following findings were made based upon renal biopsy[14].

- Minimal change disease (MCD) – 77 %
- Membranoproliferative glomerulonephritis (MPGN) – 8 %
- Focal and segmental glomerulosclerosis (FSGS) – 7 %
- Proliferative glomerulonephritis – 2 %
- Mesangial proliferation – 2 %
- Focal and global glomerulosclerosis – 2 %
- Membranous glomerulonephropathy – 2 %

Eighty percent of patients with MCD and 50 percent of patients with FSGS presented before six years of age. In contrast, none of the 39 patients with MPGN presented before six years of age.

Subsequent studies have demonstrated an increasing prevalence of FSGS. Whether this is due to a true increase in prevalence or is a result of improved detection of the histologic changes consistent with FSGS on renal biopsy is unknown. Since the diagnosis of FSGS is made by the detection of one or more glomeruli with segmental glomerulosclerosis, one cannot be certain that a patient with an initial diagnosis of MCD does not actually have FSGS that was missed because of sampling error.

The following observations illustrate the range of findings:

- In a retrospective study of 159 Canadian children with nephrotic syndrome who presented between 1985 and 2002, 115 patients (72 percent) had MCD, diagnosed by renal biopsy or response to glucocorticoid, and 29 children had FSGS (18 percent) diagnosed by renal biopsy[18]. The incidence of FSGS increased 2.5 fold during the last half compared to the first half of the study.

- In another retrospective study of 152 patients from Texas with idiopathic nephrotic syndrome diagnosed between 1978 and 1997, 37 of the 105 patients who underwent renal biopsy had MCD (35 percent) and 33 (31 percent) had FSGS[19]. If one assumed that all 47 patients who did not undergo renal biopsy had MCD, then 55 and 22 percent of the total group were estimated to have MCD and FSGS, respectively. FSGS was found in a greater percent of biopsies after 1990 compared to before (47 versus 23 percent) and was the most common diagnosis for nephrotic syndrome in African American children (63 percent).

In both of these studies, the incidence of FSGS may have been underestimated because all patients who did not undergo renal biopsy were presumed to have MCD and because FSGS can be missed on renal biopsy due to sampling error, since by definition the disease is focal (ie, only some glomeruli have sclerotic lesions on light microscopy).

DIAGNOSIS – The diagnosis of nephrotic syndrome is made by fulfilling the following two defining characteristics:

- Urinary protein excretion greater than 40 mg/m^2 /hr

- Hypoalbuminemia (< 2.5 gm/ dL)

Although, edema is generally the presenting sign of nephrotic syndrome, the diagnosis is confirmed by the presence of nephrotic range proteinuria and hypoalbuminemia.

EVALUATION OF MICROSCOPIC HEMATURIA IN CHILDREN:

INTRODUCTION – Microscopic hematuria is a common finding in children. As illustrated in two large population-based studies, 3 to 4 percent of unselected school-age children between 6 to 15 years of age had a positive dipstick for blood in a single urine sample [20,21].

There is a long list of causes of microscopic hematuria, most of which are benign, especially in children with isolated asymptomatic microscopic hematuria. The dilemma that faces the clinician is to identify the child in whom hematuria caused by significant underlying disease.

Isolated glomerular hematuria – In patients with asymptomatic microscopic hematuria (ie, persistent microscopic hematuria with dysmorphic red blood cells, negative "dipstick" for proteinuria, normal serum creatinine concentration, and normal blood pressure), the renal biopsy may not alter therapy, as such patients generally have a good prognosis. When biopsies are performed, they typically demonstrate either a normal kidney biopsy or one of three disorders: IgA nephropathy, hereditary nephritis (Alport syndrome), or thin basement membrane disease. Most patients with IgA nephropathy and thin basement membrane disease without proteinuria have a good long-term prognosis and, other than angiotensin converting enzyme inhibitors, there is no clear effective therapy for any of these conditions.

As a result, a renal biopsy is not routinely performed to establish a specific diagnosis, at least in the United States, unless there is evidence of progressive disease, such as increasing proteinuria or a rising serum creatinine concentration[22]. In a prospective study of 276 native renal biopsies, for example, biopsy for isolated hematuria changed a management decision in only one of 36

patients[4]. However, a specific diagnosis may be desired by some patients for genetic counseling purposes, such as in Alport syndrome.

DETECTION – Hematuria is defined by the presence of an increased number of red blood cells (RBCs) in the urine. Hematuria can either be visible to the naked eye (gross) or apparent only upon urinalysis (microscopic). Microscopic hematuria may be discovered as an incidental finding on an urinalysis prompted by urinary or other symptoms.

Urinary dipstick – The most common screening test for hematuria is the urinary dipstick test for blood. The reagent strip that detects blood utilizes hydrogen peroxide, which catalyzes a chemical reaction between hemoglobin (or myoglobin) and the chromogen tetramethylbenzidine. Different shades of blue-green are produced according to the concentration of hemoglobin in the urine sample. These strips can detect 5 to 10 intact RBCs/μL, which roughly corresponds to a finding on microscopic examination of two to five RBCs per high-power field from the sediment of a centrifuged 10 to 15 mL urine sample.

False-negative results can occur in the presence of formalin or high urinary concentration of ascorbic acid. False-positive results may occur with alkaline urine (ie, pH greater than 9) or contamination with oxidizing agents used to clean the perineum.

Microscopic examination – A positive dipstick for hematuria is confirmed by a microscopic examination of the sediment of 10 to 15 mL of centrifuged fresh urine. Microscopic hematuria is defined as the presence of more than five RBCs per high-power field (40x magnification)[23,24].

The microscopic examination is the gold standard for the detection of microscopic hematuria. Dipsticks for hemoglobin are as sensitive as the urine sediment examination, but result in more false-positive tests. In comparison, false-negative dipstick tests are unusual; as a result, a negative dipstick reliably excludes abnormal hematuria.

The procedures for obtaining and processing urine samples in children are reviewed separately.

Glomerular versus nonglomerular bleeding – Urinalysis including microscopic examination may identify a potential site of bleeding (glomerular versus nonglomerular) and aid in determining the underlying cause. The identification of the glomeruli as the source of blood is important both prognostically and to optimize the subsequent diagnostic evaluation.

Signs of glomerular bleeding in children with microscopic hematuria include the following:

- Red cell casts (pathognomonic for glomerular disease)
- Protein excretion greater than 100 mg/m^2 at a time when there is no gross bleeding. The optimal method is obtaining a first morning sample to determine the protein to creatinine ratio because it excludes orthostatic proteinuria, a normal variant.
- Red blood cells (RBCs) having a dysmorphic appearance[25].

Although helpful if present, the absence of these findings does not exclude glomerular disease.

Morphologic study of urinary RBCs, particularly with a phase-contrast microscope, may be helpful in distinguishing glomerular from nonglomerular bleeding. The presence of more than 30 percent dysmorphic RBCs or of more than 5 percent of a specific form named an "acanthocyte" is highly suggestive of glomerular hematuria. However, confident identification of such cells requires expertise in urinalysis.

In nonglomerular hematuria, microscopic examination demonstrates urinary RBCs with a uniform normal size and shape. However, hypercalciuria, a nonglomerular cause of hematuria, can be associated with dysmorphic red blood cells but not red cell casts.

EPIDEMIOLOGY – Several population-based studies of unselected school-age children have shown that the prevalence rate for microscopic hematuria detected in a single urine sample is 3 to

4 percent, which falls to 1 percent or less for two or more positive samples[20,21,26]. Among the 1 percent of children with two or more positive urines for hematuria, only one-third have persistent hematuria, defined as a positive repeat test after six months[20,21].

The combination of hematuria and proteinuria is less common with a prevalence rate of less than 0.7 percent in unselected school-age children in a single urine sample[20,21].

ETIOLOGY – Both benign and serious conditions can cause microscopic hematuria in children. The most common causes of persistent microscopic hematuria include glomerulopathies, hypercalciuria, and nutcracker syndrome[23].

- IgA nephropathy – IgA nephropathy is diagnosed by renal biopsy with mesangial IgA deposits on immunofluorescence study There is often a history of gross hematuria preceded by an upper respiratory tract or gastrointestinal illness and usually a negative family history of renal disease.
- Alport syndrome – Classic Alport syndrome (hereditary nephritis) is a recessive X-linked disorder that is typically seen in males and is often accompanied by high-frequency sensorineural hearing loss, ocular abnormalities including anterior lenticonus, and, over time, progressive renal failure Heterozygous carrier-females also can have hematuria, but do not have progressive renal disease.

- Thin basement membrane disease (TBM) – TBM, also called benign familial hematuria, is an autosomal dominant condition. Kidney biopsy reveals an isolated thinning of the glomerular basement membrane on electron microscopy . In many cases, TBM disease is the heterozygous form of autosomal recessive Alport syndrome involving the COL4A3 or COL4A4 genes; two abnormal genes are required for the Alport phenotype.

- Postinfectious glomerulonephritis – In children with poststreptococcal glomerulonephritis, hematuria generally resolves within three to six months after the presentation.
- Hypercalciuria – Hypercalciuria, defined in children as a urine calcium/creatinine ratio >0.2 (mg/mg) in children older than six years of age, has been associated with asymptomatic microscopic hematuria. In studies performed in the United States, the prevalence has ranged from as low as 11 percent in the Northeast[27] to as high as 35 percent in the South[28,29]. Thus, the association between hypercalciuria and hematuria may be more common in areas where there is a higher prevalence of nephrolithiasis.

EVALUATION – The diagnostic evaluation depends upon the clinical presentation, which falls into the following three categories:

- Asymptomatic isolated microscopic hematuria
- Asymptomatic microscopic hematuria with proteinuria
- Symptomatic microscopic hematuria .

Distinguishing extraglomerular from glomerular hematuria

	Extraglomerular	**Glomerular**
Color (if macroscopic)	Red or pink	Red, smoky brown, or "Coca-Cola"
Clots	May be present	Absent
Proteinuria	Usually absent	May be present
RBC morphology	Normal	Dysmorphic
RBC casts	Absent	May be present

Asymptomatic isolated microscopic hematuria – As noted above, asymptomatic isolated microscopic hematuria (ie, no proteinuria) is present in 3 to 4 percent of unselected school-age

children[20,21,26]. However, significant clinical disease is rarely detected. This was illustrated in a 1979 study of an unselected population of 8954 children who were screened for hematuria.

The following approach can be considered for children with asymptomatic isolated microscopic hematuria based upon the available literature[20,21,23,45].

- Evaluation including blood pressure measurement and a urinalysis should be performed weekly for two weeks. One should ensure that there is no exercise prior to obtaining the urine sample, since vigorous exercise can induce hematuria. A thorough evaluation should be undertaken only if the patient becomes symptomatic or develops hypertension, gross hematuria, or proteinuria.
- If isolated hematuria persists, obtain a urine culture. If the culture is positive, treat with appropriate antibiotics.
- If the patient remains asymptomatic and the urine culture is negative, continue to observe the patient every three to six months including physical examination with blood pressure measurement and urinalysis.
- If the asymptomatic isolated hematuria persists for one year, the following subsequent evaluation should be performed:

- Measure urine calcium/creatinine ratio for hypercalciuria. Hypercalciuria, defined as a urine calcium/creatinine ratio >0.2 (mg/mg), has been associated with asymptomatic microscopic hematuria.

There is disagreement as to whether children with hypercalciuria have an increased likelihood of a family history of nephrolithiasis and whether hypercalciuria leads to renal stones[27,28,29]. Although lowering urinary calcium excretion with a thiazide diuretic can lead to

resolution of the hematuria[29], there is at present no consensus on the further evaluation or treatment of children with isolated microscopic hematuria who have hypercalciuria.

Asymptomatic microscopic hematuria and proteinuria – The combination of hematuria and proteinuria is significantly less common than either isolated proteinuria or hematuria. Although asymptomatic hematuria with proteinuria has a prevalence rate of less than 0.7 percent in unselected school-age children, it is associated with a higher risk for significant renal disease[20,21,24,30].

Evaluation of these patients starts with measurement of serum creatinine and quantification of proteinuria either by a 24-hour urine collection or determination of the urine protein-to-creatinine ratio on a first morning urine sample.

- If protein excretion is >4 mg/m^2 per hour or if in a first morning urine specimen, the urine protein-to-creatinine ratio is >0.2 mg protein/mg creatinine in children older than 2 years of age and >0.5 mg protein/mg creatinine in younger children, the patient should be referred to a pediatric nephrologist (or a clinician with expertise in the care of children with renal disease) since it is likely that there is significant renal disease.
- If protein excretion is less than the above values, the patient should be reevaluated in two to three weeks.

- If the hematuria and proteinuria have resolved, no further evaluation is needed.
- If there is only asymptomatic microscopic hematuria, the patient is monitored in the same fashion as those described above with asymptomatic isolated microscopic hematuria.
- If proteinuria is persistent the patient should be referred to a pediatric nephrologist (or a clinician with expertise in the care of children with renal disease) for further evaluation.

- Patients with significant proteinuria or an elevated serum creatinine at baseline, or persistent proteinuria at follow-up should be referred to a pediatric nephrologist (or a clinician with expertise in the care of children with renal disease) because they are likely to have renal disease. Further assessment should include microscopic examination of the urine by an experienced clinician, serum creatinine, C3, C4, albumin, and complete blood count. Depending upon the findings, other tests that may be considered include ASO titer, streptozyme testing, antinuclear antibody testing, imaging, and renal biopsy.

Symptomatic microscopic hematuria – The evaluation of symptomatic microscopic hematuria is directed by the patient's symptoms and clinical findings. This category is the most challenging because it encompasses a wide range of diseases with varying clinical presentations[23,31]. The clinical manifestations may be nonspecific (eg, fever, malaise, weight loss), extrarenal (eg, rash, purpura, arthritis), or related to kidney disease (eg, edema, hypertension, dysuria, oliguria).

The presence of nonspecific or extrarenal manifestations suggests a systemic process such as lupus nephritis or Henoch-Schönlein purpura. Renal causes of symptomatic microscopic hematuria include glomerular or interstitial diseases of the kidney, lower urinary tract disease, nephrolithiasis, tumors, and vascular disease.

The diagnosis may be evident and straightforward from the history and physical examination. The urinalysis can be helpful in differentiating between glomerular and nonglomerular causes of bleeding.

Indications for renal biopsy – A renal biopsy is not usually performed for isolated microscopic hematuria. However, biopsy should be considered if there is evidence of substantial or progressive disease as manifested by an elevation in the creatinine concentration, significant proteinuria, or an otherwise unexplained rise in blood pressure even when the values remain

within the normal range. Biopsy also may be considered in the child with persistent glomerular hematuria, in whom the parents are worried about the diagnosis and prognosis. In addition, a kidney biopsy may be considered in a child with microscopic hematuria and a family history of kidney failure in early adulthood in a first order relative.

Patients with clear evidence of poststreptococcal glomerulonephritis represent an exception to these general recommendations, since gradual spontaneous recovery is the rule, although proteinuria may gradually return to normal over many years.

Acute nephritic syndrome – Hematuria, cellular casts, proteinuria, and frequently hypertension and renal insufficiency – is often caused by a systemic disease that requires a renal biopsy to establish the diagnosis and guide treatment. However, there are situations in which the initiation of therapy is required while awaiting the renal biopsy. Examples include microscopic polyangiitis, Wegener's granulomatosis, or anti-GBM disease. These are disorders that are associated with rapidly progressive glomerulonephritis and, in the appropriate clinical setting, are suggested serologically by the presence of circulating antineutrophil cytoplasmic antibodies (ANCA) or anti-GBM antibodies.

The reason for a biopsy is variable in lupus nephritis. Patients with acute renal insufficiency and an active sediment may have any number of lesions and require a renal biopsy to establish a diagnosis, determine prognosis, and guide therapy.

Another indication for renal biopsy is an intermediate clinical presentation – mild proteinuria and hematuria, or nephrotic syndrome with a bland sediment. In this setting, the diagnosis may be focal or diffuse proliferative disease or membranous lupus, each of which may require different forms of therapy. A repeat biopsy may also be performed for late progression of the disease to distinguish between active lupus (which may require immunosuppressive therapy) and scarring

of previous inflammatory injury (which may warrant antihypertensive therapy with an angiotensin converting enzyme inhibitor).

Unexplained acute renal failure – The most common causes of acute renal failure – prerenal disease, acute tubular necrosis, and urinary tract obstruction – can be diagnosed without renal biopsy. Biopsy is indicated in those settings in which the diagnosis is uncertain, as may sometimes be the case with acute interstitial nephritis secondary to drugs[9]. By comparison, patients with small kidneys or slowly progressive chronic renal failure over a period of years are generally not biopsied since there is little likelihood of finding a treatable disease.

OVERVIEW OF SPECIFIC ISSUES IN PAEDIATRIC RENAL BIOPSY PATHOLOGY

Congenital/infantile nephrotic syndrome

Children presenting with nephrotic syndrome in the first 3 or 6 months of life are considered to be suffering from some form of CNS, and additional cases will present during the infantile period. There are traditionally two major pathomorphological subtypes of CNS: Finnish-type (associated with nephrin gene mutations) and French-type, now more commonly referred to as diffuse mesangial sclerosis (associated with WT1 or unknown mutations).

It is apparent that infants with congenital/ infantile nephrotic syndrome may also exhibit a variety of other glomerulopathies, including otherwise unspecified diffuse mesangial proliferative glomerulonephritis and idiopathic primary FSGS variants, in addition to the traditional CNS subtypes , some of which may respond to treatment with angiotensin-converting enzyme inhibitors[32]. CNS may rarely be associated with other specific

aetiologies such as congenital infections including cytomegalovirus (with a diffuse mesangial sclerosis pattern in association with viral inclusions, which may respond to antiviral treatment)[33], syphilis and toxoplasmosis[34].

Furthermore, it is now apparent that these categories of disease, including the apparently well-described Finnish-type CNS and diffuse mesangial sclerosis, may be both morphologically and genetically heterogeneous. Classical Finnish-type CNS is an autosomal recessive disorder caused by mutations in the nephrin gene (NPHS1), a component of the glomerular slit diaphragm, and more than 50 mutations have been reported, including two predominant nonsense mutations in Finnish patients and a range of missense, nonsense and splice-site mutations, as well as deletions and insertions, predominantly in non-Finnish groups[35,36]. Additional mutations of other genes also involved in slit diaphragm structure, such as podocin, are now recognised as being of increasing importance in determining the phenotype of CNS[37]. CNS may also rarely be a presentation of other systemic disorders, such as mitochondrial respiratory chain deficiency, in which the pathological phenotype may mimic Finnishtype CNS but without associated nephrin mutations[38], and infantile lupus[39]. From a practical perspective, the diagnostic pathologist faced with a biopsy to interpret should be aware that the classical 'textbook' features of these conditions may not be readily apparent in a needle-core biopsy obtained early in the disease course, and conversely, with disease progression, secondary glomerular and tubulointerstitial changes may also make the specific diagnosis difficult in such core biopsy material. The main aim of biopsy in this setting is therefore to exclude other subtypes of nephrotic-associated glomerulopathy, which may be amenable to therapeutic intervention, and to make a specific diagnosis where possible.

Finnish-type CNS is classically characterised by glomeruli that are initially morphologically unremarkable but may develop mild dilation of Bowman's space, with associated scattered characteristic tubular microcyst formation owing to dilation of the proximal tubular components.

With disease progression, cyst formation may become more prominent and there are superimposed secondary changes of glomerulosclerosis, tubular atrophy and interstitial fibrosis, which are often readily apparent in cases coming to nephrectomy. In contrast, diffuse mesangial sclerosis is characterised by widespread glomerular sclerosis, with many glomeruli appearing small and shrunken, many being virtually replaced by hyaline nodules. In this setting, the peripheral glomeruli are most severely affected, in contrast to idiopathic FSGS in which the deep juxtamedullary glomeruli are characteristically most severely involved.

The main aim of biopsy in this setting is to determine the underlying diagnosis in order to direct further therapy and assess prognosis, the main differential diagnosis being MCD versus other causes of paediatric nephrotic syndrome such as idiopathic FSGS, and other rarer entities[40]. Since the deep juxtamedullary glomeruli are initially preferentially affected in primary FSGS, comment should be made on whether the biopsy includes this deep cortical zone, particularly in cases in which no histological abnormalities are seen on light microscopy. Furthermore, it should be remembered that any area of tubular atrophy is a significant finding in a paediatric renal biopsy, and in this context such a finding should raise the suspicion of an associated focal segmental sclerotic lesion, so serial sections should be examined. It is noteworthy that, in contrast to adult practice, primary membranous nephropathy is extremely uncommon in childhood, although well reported. The histological features are identical to those seen in adults, with secondary membranous change in the setting of lupus nephritis being more frequent in centers dealing with patients with autoimmune disease.

For example, in two studies including more than 300 children biopsied for steroid-resistant or atypical nephritic syndrome, FSGS was diagnosed in around 40%, followed by minimal-change nephropathy (20–30%), MPGN (15%), mesangial proliferative (10%) and membranous (5%). In younger children, however, MCD was the most common entity, whereas

FSGS predominated in the older children[41,42]. In addition, it has been reported that the frequency of FSGS is increasing, but it remains uncertain whether this represents a true increase in prevalence or is simply a consequence of changing biopsy indications, referral practices or criteria for diagnosis on the part of pathologists. Other specific morphological causes of nephritic syndrome are unusual, but it should be noted that both familial and HIV-associated collapsing glomerulopathy are recognised in childhood with similar histological features to the adult counterpart (collapsed, sclerosed glomeruli with prominent glomerular epithelial cells and associated tubular dilation), and poor renal prognosis with rapid progression. Other conditions that may present with nephrotic syndrome (usually mixed nephritic/ nephrotic) in this group of patients are dense deposit disease, a diagnosis that requires electron microscopic examination for definitive confirmation and membranoproliferative glomerulonephritis, the features of which are identical to those in adults.

A prediction of the long-term response to therapy and the outcome in paediatric nephrotic syndrome is difficult, the major prognostic factor overall being the initial response to steroids[40]. In those undergoing renal biopsy, the presence of FSGS is associated with a, increased risk of progression to renal failure, but within this subgroup there is a relatively poor association between the histopathological findings and the prediction of outcome in an individual patient. In general, the extent of glomerulosclerosis and chronic tubulointerstitial changes is most strongly associated with subsequent adverse outcome, but other features such as associated immune deposition or mesangial expansion appear to show no consistent relationship with disease progression and outcome[43]. After proteinuria, apparently isolated haematuria is next most common indication for renal biopsy in childhood. The most frequent diagnoses in this group of patients include congenital abnormalities of the glomerular basement membranes, IgA

nephropathy and other glomerulonephritides, most of which are associated with coexisting proteinuria or other manifestations.

Since Alport syndrome and TGBM nephropathy are relatively common in this context, it is obviously essential that all such biopsies undergo routine electron microscopic examination. Although ultrastructural examination is diagnostic, it should be noted that the characteristic 'basketweave' basement membrane change of Alport syndrome may not always be present in children, and the only finding initially may be diffuse thinning of the basement membrane. Hence the possibility of Alport syndrome should not be excluded on a single renal biopsy finding of apparently isolated basement membrane thinning, particularly if other suggestive clinical or morphological features are present. Furthermore, there may be a variation in basement membrane thickness, and the subjectively thinned areas should be targeted. Although normal ranges are available for glomerular basement membrane thickness by age and sex in childhood[44], it is suggested that each centre use its own derived age-related normal ranges as there may be variability in measurement techniques and processing methods. Acute renal failure In the setting of acute renal failure in childhood, the most common associated conditions of those children who come to biopsy are vasculitic, such as Henoch–Scho¨nlein nephritis and Wegener's granulomatosis, systemic diseases such as lupus erythematosus and other glomerulonephritides such as MPGN and diffuse endocapillary proliferative post-infectious glomerulonephritis.

Acute interstitial nephritis may also occasionally be biopsied in this setting, particularly if the features and clinical history are atypical, and thrombotic microangiopathies such as haemolytic uraemic syndrome are also encountered. The pathological features of these conditions are essentially identical to those described in the adult literature.

In addition to establishing the primary diagnosis, the biopsy should be processed urgently in this clinical setting as treatment may depend upon the extent of disease activity, particularly in the

vasculitic conditions in which the extent and type of crescents present may be used to stratify further clinical management protocols. It should be noted, as above, that children with nephrotic syndrome may develop acute oliguria when dehydrated, and acute renal deterioration in such patients should also raise the possibility of superimposed renal vein thrombosis.

Childhood Lupus Nephritis:

Systemic lupus erythematosus (SLE) is an autoimmune disease that involves multiple organs, causing severe morbidity and mortality. While the incidence of childhood SLE is relatively low, renal involvement appears to be more common and severe in children than in adult SLE patients[45,46,47.] It has been reported that more than 70% of children diagnosed with SLE develop lupus nephritis (LN) at the early stage of the disease[47,48,49]. Recently, improved treatment outcomes for children with LN have been reported. Pediatric studies on LN showed a 5-year patient and renal survival rate of more than 83% and 63%, respectively[50,51,52,53.] These results might be due to more extensive use of cytotoxic agents in addition to corticosteroids (CSD) in severe LN cases[54,48,49]. However, it has not been established which cytotoxic agent is most responsible for this improvement in renal and patient survival in pediatric LN.

After the reports from the National Institutes of Health (NIH) study group[55,56] intravenous cyclophosphamide (CPM) pulse therapy has been widely accepted as the 'gold standard' treatment for diffuse proliferative LN, not only in adults but also in children. However, recent controlled trials have been unable to demonstrate the superiority of prolonged CPM pulse therapy over other immunosuppressants added to the CSD treatment in the management of severe LN[57,58,59.] Likewise, while some pediatric reports claimed better renal survival rates in patients undergoing long-term CPM pulse therapy[51], other reports did not[60].

AIMS AND OBJECTIVES OF THE STUDY:

1. To study the distribution of various renal diseases in pediatric age group in our center
2. To analyze patient characteristics, clinical and biochemical parameters among each group of biopsy proven renal diseases.
3. To study the various modality of treatment and its out come among these patients.

PATIENTS AND METHODS:

This study included all paediatric patients (age between 0 -18 years) with biopsy proven renal disease between 1997 -2006 in Christian Medical College, Vellore, a tertiary referral center in South India.

Inclusion criteria: Patients between 1 month -18 years of age & Biopsy proven renal diseases

Exclusion criteria: Patients more than 18 years of age & Those patients who have undergone renal transplantation

Evaluation and Study design:

First, the type of renal disease based on biopsy was categorized. Among each group of renal disease, detailed demographic parameters of each patient was documented and patients were analyzed separately to look for multiple clinical and biochemical parameters. The light microscopic picture, response rate, relapse rate and medications used were separately analyzed for each group of diseases. Patients less than 10 years of age underwent biopsy procedure under general anaesthesia.

Statistical analysis:

Data were analyzed using SPSS version 15 Inc. (Chicago, USA). Standard statistical methods for assessment on proportions, percentages and measures of central tendencies (mean, SD, median and range).

DEFINITIONS :

International Study of Kidney diseases in Children.

Nephrotic syndrome is defined as heavy proteinuria (> 40 mg / hr /m^2) determined quantitatively on an overnight collection of urine, accompanied by hypoalbuminaemia (2.5 g/dl).

Proteinuria is considered to be in the nephrotic range when the

- ✓ urine protein is 3+/4+ on a dipstick test,
- ✓ spot protein/creatinine ratio >2 mg/mg, or
- ✓ urine albumin >40 mg/m^2/ hr (on a timed sample).

OUTCOME MEASURES:

- **Response** – reduction of urinary excretion of protein to <4 mg/h/m^2 or albustix of 0 to trace for 3 consec. days
- **Relapse** – appearance of proteinuria ≥ 40 mg/h/m^2 or albustix of ≥ 2+ for 3 consec. days
- **Initial Responder** – patient who responds during 8 weeks of initial regimen
- **Initial Non responder** – patient who failed to respond during the first 8 weeks of treatment
- **Late Responder** – Initial nonresponder who responded after some time after the first 8 weeks of prednisolone therapy
- **Late Non responder** – Initial responder who subsequently failed to respond
- **Early Relapser** – Initial responder who relapsed during the initial 8 weeks therapy itself
- **Frequent Relapser** – An initial responder who has 2 or more relapses within first 6 months of initial response.

RESULTS:

- **Duration of study – Between January 1997 and December 2006**
- **Total no of biopsies – 1480.**
- **Data analyzed – 887 (583 excluded due to unavailability of data)**
- **Age group – Between 1 Month to 18 years.**

Total number of paediatric renal biopsies done at CMC Vellore during the time period 1997 and 2006 were 1480.Out of which 887 patients data were analyzed. In the others the records were not available. The age group were from 1 month upto to 18 years of age.

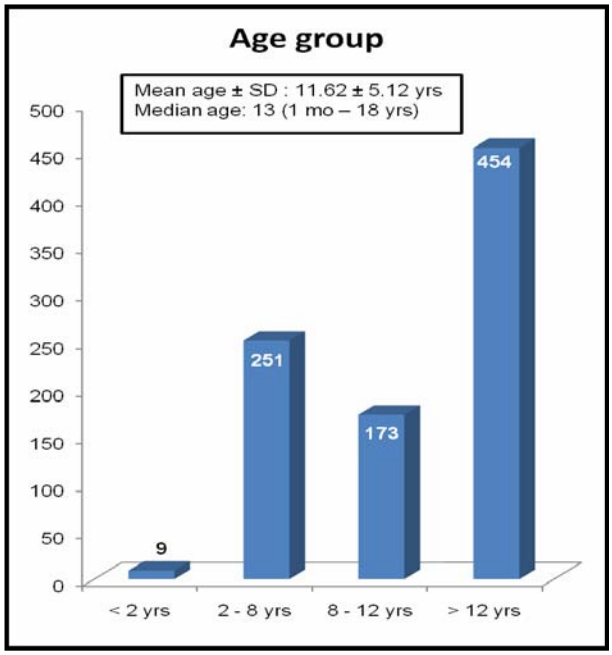


Figure 1

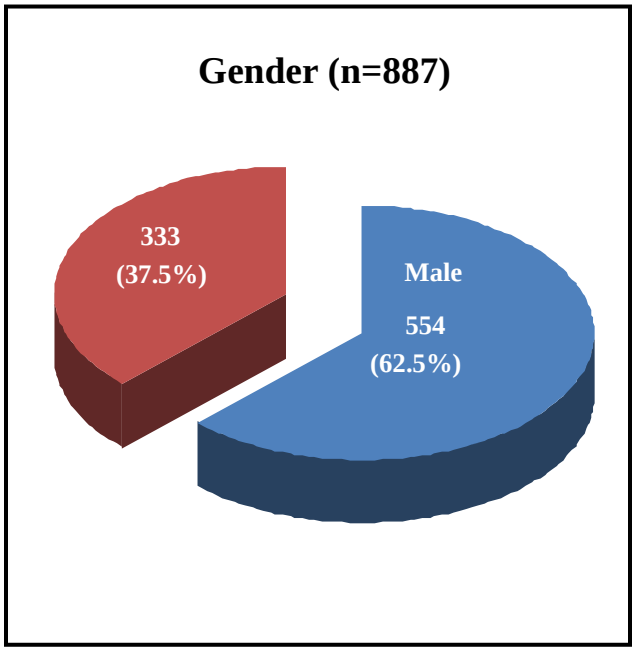


Figure 2

The mean age was 11.62 ± 5.12 yrs with range of 1-18 yrs. Majority of the children were above 12 years of age. Male children constituted 554 (62.5 %).

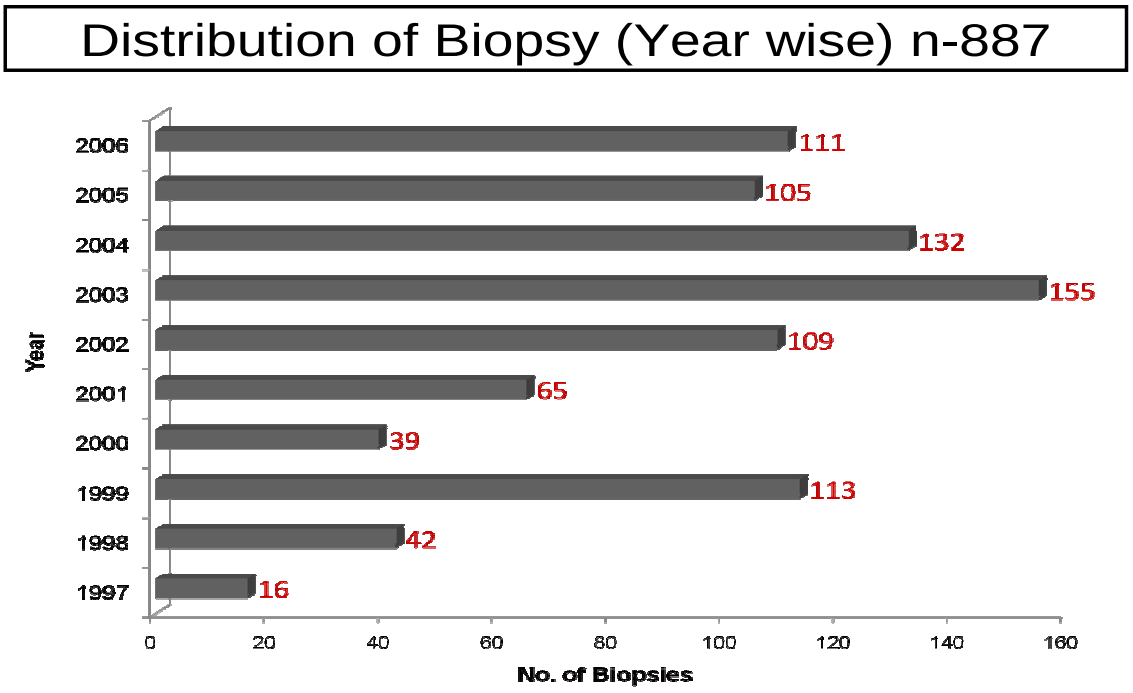


Figure 3: Shows the year wise distribution of renal biopsy.

Table 1: Various clinical syndromes

Clinical Syndromes (n=887)	Percentage
Nephrotic Syndrome (n- 611)	68.6%
Nephritic Syndrome (n- 211)	25.3%
Rapidly progressive renal failure (n- 22)	2.5%
End Stage Renal Disease (unknown etiology),(n-14)	1.6%
Asymptomatic hematuria (n- 15)	0.8%
Acute Renal failure (n- 4)	0.4%
Subnephrotic proteinuria (n- 2)	0.2%
Others (Alports syndrome), (n- 8)	0.6%

Table -2: Different histopathological diagnoses with clinically diagnosed Nephrotic Syndrome.

Nephrotic syndrome (n=611)	Number (%)
Minimal change disease	291 (47.6%)
Mesangial proliferative GN(non IgA)	111 (18%)
Focal Segmental Glomerulosclerosis	55 (9%)
Diffuse mesangial hypercellularity	53 (8%)
Proliferative GN	24 (3.9%)
Membranous GN	23 (3.7%)
Mesangial proliferative IgA Nephropathy	20 (3.2%)
Lupus nephritis	15 (2.4%)
Membrano proliferative GN	7 (1.1%)
Vasculitis,granulomatous interstitial nephritis, End stage kidney disease.	5 (0.8%)

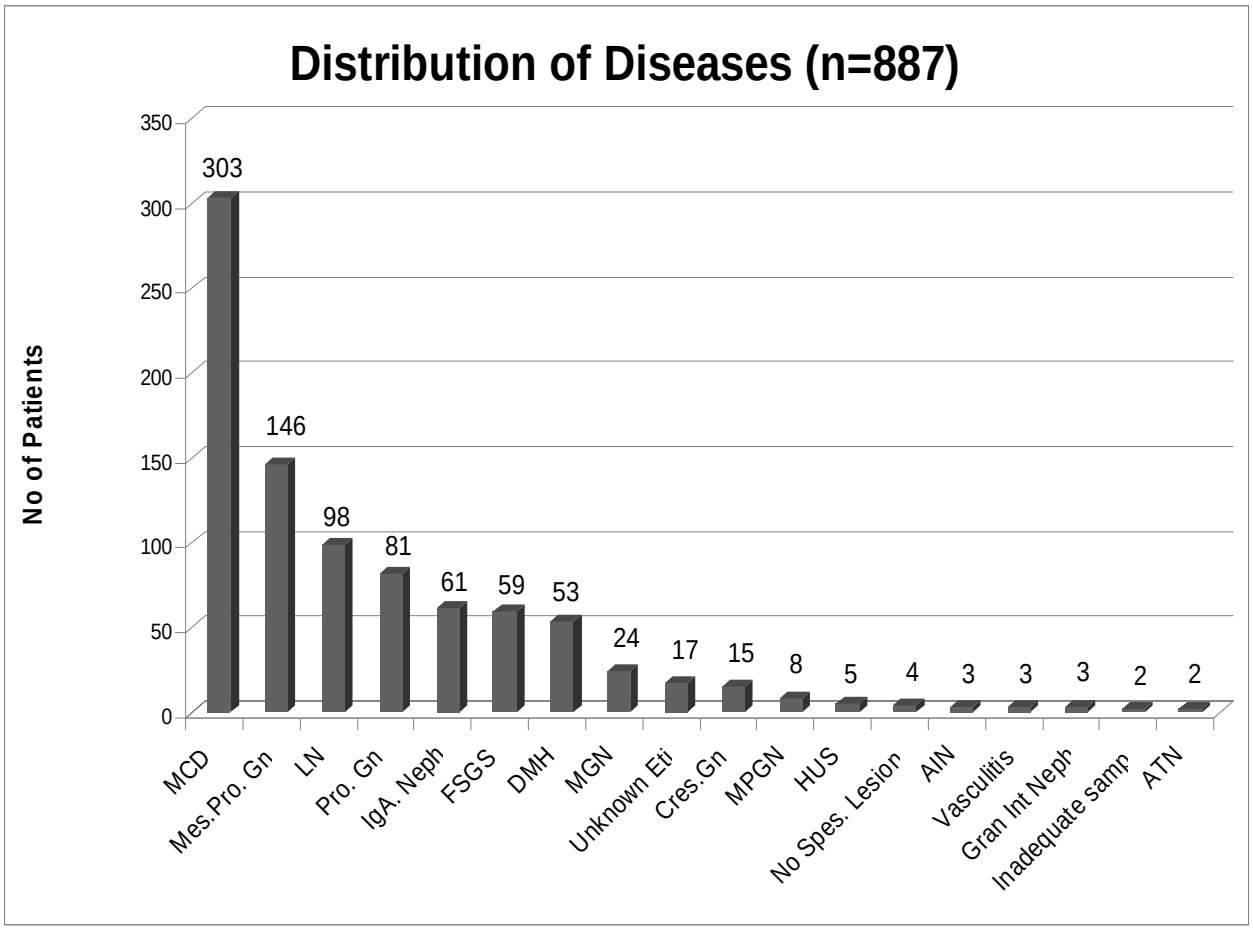
Table 3: Various histopathological diagnoses with clinically diagnosed Nephritic Syndrome.

Nephritic syndrome (n=211)	Number (%)
Lupus nephritis	80 (37.9%)
Acute Proliferative GN	51 (24.1%)
IgA Nephropathy	38 (18%)
Mesangial proliferative GN	32 (15.1%)
Crescentic GN, FSGS,Vasculitis, AIN, HUS, End stage kidney disease.	10 (0.47%)

Table -4: Various histopathological diagnoses with clinically diagnosed Rapidly Progressive Renal Failure.

Rapidly Progressive Renal Failure (n=22)	Number (%)
Crescentic GN	12 (54.54%)
Proliferative GN	4 (18.18%)
FSGS	2 (9.09%)
Mesangial proliferative GN, IgA nephropathy, AIN, End stage kidney disease	1 each

Fig 4



Minimal change disease was 303(34.16%),Mesangial proliferative GN was 146 (16.45%), Lupus nephritis was 98(11.05%), Proliferative glomerulonephritis was 81(9.13%), IgA nephropathy was 61 (6.87%), Focal segmental glomerulosclerosis was 59(6.65%), Diffuse mesangial hypercellularity was 53(5.97%), Membranous glomerulonephropathy was 24(2.70%),Crescentic glomerulonephritis was 15(1.69%), Membrano proliferative glomerulonephritis was 8(0.9 %),Hemolytic uremic syndrome was 5 (0.56 %),Vasculitis was 3(0.33 %), Acute interstitial nephritis was 3 (0.33%), Acute tubular necrosis was 2(0.22 %), granulomatous interstitial nephritis was 3(0.33%),End stage etiology of unknown etiology were 17(1.92 %), Inadequate sample was 2 (0.22%).

Table 5: Geographic distribution of patients from different states of India.

Sl No	State	No of patients	Percentage
1	West Bengal	344	38.8
2	Tamil Nadu	148	16.7
3	Jharkhand	87	9.8
4	Bihar	49	5.5
5	Kerala	46	5.2
6	Bangladesh	43	4.8
7	Assam	28	3.2
8	Andhra pradesh	26	2.9
9	Orissa	20	2.3
10	Arunachal pradesh.	11	1.2
11	Karnataka	10	1.1
12	Chhatisgarh	9	1.0
13	Madhya pradesh	9	1.0
14	Bhutan	9	1.0
15	Tripura	8	0.9
16	Meghalaya	7	0.8
17	Mizoram	7	0.8
18	Manipur	6	0.7
19	Nepal	7	0.8
20	Uttar pradesh	4	0.5
21	Maharastra	2	0.2
22	Nagaland	2	0.2
23	Maldives	2	0.2
24	C handigarh	1	0.1
25	Jammu & kashmir	1	0.1
26	Sikkim	1	0.1

DISTRIBUTION ,DEMOGRAPHIC DETAILS,TREATMENT & OUTCOME OF VARIOUS TYPES OF DISEASES IN CHILDHOOD.

Table 6: **Different characteristics of Minimal Change Disease**

Minimal change disease (MCD) n = 303	Characteristics
Gender (M:F)	3:1
Age (Mean ± SD, Range)	8.48 ± 4.7, 1-18
Nephrotic: Subnephrotic	184: 92 (valid 276)
Time for remission (Median days; range)	209, 8 – 3408
Follow up in days (Median; Range)	464, 28 – 3618
Creatinine (Mean ± SD, Range)	0.58 ± 0.24, 0.3 – 2.9mg%
24 Hr Urine protein (Median, Range)	639.5.6 mg – 19.5 gm
Serum albumin (Mean ± SD, Range)	2.7 ± 1.2, 0.3 – 4.9gm
Hypercholesterolemia	138 (74.6%) valid for 185 pt only

Among the various diseases in childhood minimal change disease was the majority, contributing to 34.16%.

Table 6: shows that the mean age was 8.48 ± 4.7(1-18 years), male children were the maximum in number.184 patients had nephrotic range proteinuria. The mean serum albumin was 2.7 ± 1.2 (0.3 – 4.9 gm), median 24 hr urinary protein was 639 mg. The median time for remission was 209 days. The median duration of follow up was 464 days.

Table 7: Treatment received (before presenting to this institute)

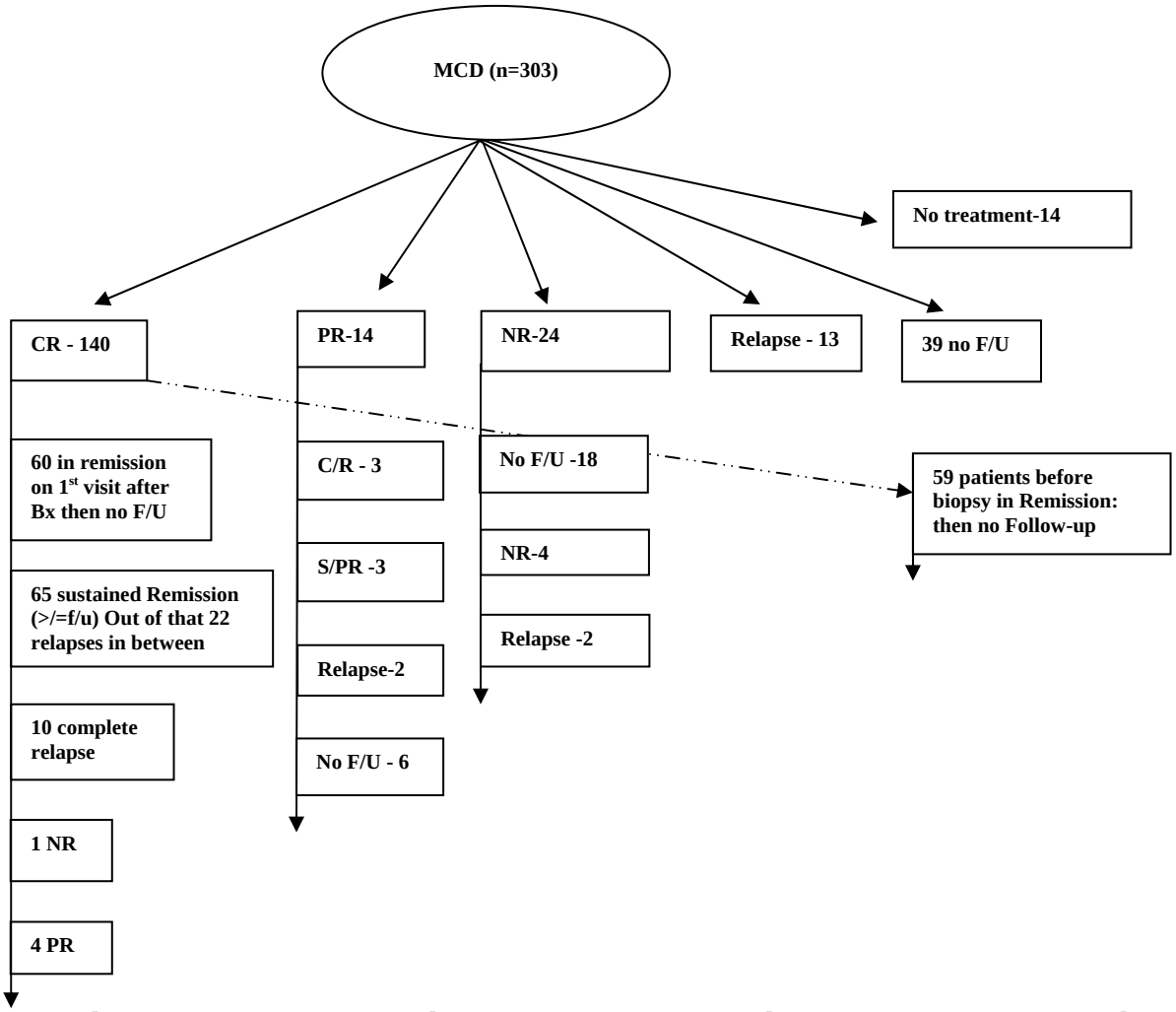
Drug	Frequency (N)	Percentage (%)
No Treatment	41	13.5
Prednisolone	250	82.5
Prednisolone + levamisole	4	1.3
Prednisolone + Cyclophosphamide	4	1.3
Cyclophosphamide	1	.3
Prednisolone + Azathioprine	1	.3
Prednisolone + Cyclophosphamide + Azathioprine	1	.3
Levamisole	1	.3
Total	**303**	**100.0**

Table 7 shows the distribution of patients who had been treated with different drugs before presenting to us. Out of 303 cases, 250 (82.5%) patients were treated with prednisolone whereas 4 patients (1.3%) each were treated with a combination of prednisolone with cyclophosphamide and prednisolone and levamisole. Forty one (13.5%) patients had not received any treatment before presenting to us.

Table -8: Various histological variant of minimal change disease by light microscopy in this study.

Disease	Frequency	Percent
MCD	30	9.9
MMH	263	86.8
MMH + AIN	1	0.3
MMH + Interstitial changes	4	1.3
MMH + Incipient sclerosis	5	1.7
Total	303	100.0

Figure 5: Outcome of children with Minimal change disease



CR – Complete remission ; PR – Partial remission ; SR – Sustained remission; SPR – Sustained partial remission ; NR – No remission; No F/U – No follow up.

Out of 303 children with MCD, 199 (65.67%) patients achieved complete remission, 14 (4.62%) patients achieved partial remission, 48 (15.84%) patients did not achieve remission, 13 (4.29%) patients had relapse, 39 (2.97 %) patients did not have follow up after biopsy, however another 59(19.47%) patients who were in remission during biopsy also did not follow up after biopsy.

Among the complete remission group 109 (54.77%) patients were only on steroid during the first revisit after biopsy. Rest were on various medication like, 47(23.61%) patients were on combination of steroid & cyclophosphamide. 2 patients were on steroid & tacrolimus,10 (5.02%)

patients were on steroid & cyclosporine,16 (8.04%) patients were on levamisole,1 patient was only on cyclosporine.6 patients were not on any medication.

On final follow up 65 patients were in sustained remission and 10 children had relapse.

Out of 48 patients which did not achieve remission 44(14.52%) patients were only on steroid.

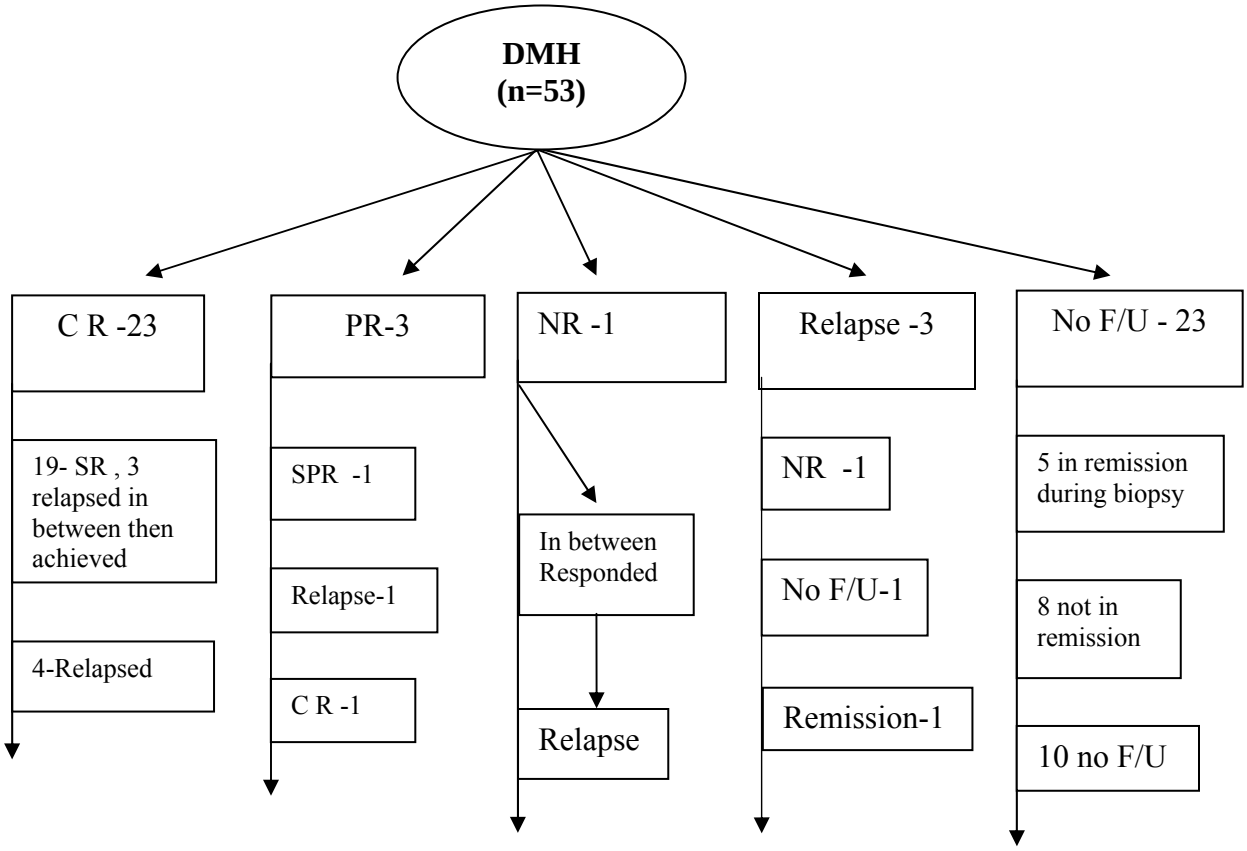
3 patients were on combination of steroid & cyclophosphamide, 1 patient was on only cyclophosphamide.

Table 9: Various characteristics of diffuse mesangial hypercellularity.

Diffuse Mesangial Hypercellularity (DMH) (n =53)	Characteristics
Gender (M:F)	1.5 : 1
Age (Mean ± SD, Range)	9.3 ±5.12, 0.1-18
Nephrotic: Subnephrotic	26: 22 (valid 48)
Time for remission (Median days, range)	212, 59 – 1294
Followup in days (Median Range)	106.8, 71 – 2693
Creatinine (Mean ± SD, Range)	0.61 ± 0.16, 0.3 – 1.1mg%
24 Hr Urine protein (Median, Range)	1300, 10mg – 18.4 gm
Serum albumin (Mean ± SD, Range)	2.24 ± 1.11, 0.8 – 4.7gm
Hypercholesterolemia	29 (85.3%) valid for 34 pt only

Table 9 shows the various characteristics of diffuse mesangial hypercellularity. The mean age was 9.3 ± 5.12 (0.1 – 18yr),male children were the maximum in number. The mean serum albumin was 2.24 ± 1.11(0.8 – 4.7gm),The mean creatinine was 0.61 ± 0.16 (0.3 – 1.1 mg%) median 24 hr urinary protein was 1300 mg. The median time for remission was 212 days. The median duration of follow up was 106.8 days.

Figure-6: Outcome of children with Diffuse Mesangial Hypercellularity



CR – Complete remission ; PR – Partial remission ; SR – Sustained remission; SPR – Sustained partial remission ; NR – No remission; No F/U – No follow up.

Figure 6 shows the treatment out come of diffuse mesangial hypercellularity . Among 53 patients of diffuse mesangial hypercellularity 23 (43.39%) achieved complete remission,3 (5.66%) patients achieved partial remission,1 (1.88%) patient did not achieve remission, 23 (43.39%) patients did not come for follow up. Among the complete remission group 9 (39.13%) patients were treated with only steroid,9 (39.13%)patients were on combination of steroid & cyclophosphamide,1 patient was on steroid & mycophenolate,4 patients were on combination of steroid & levamisole.

Table 10: Characteristics of focal segmental glomerulosclerosis (FSGS).

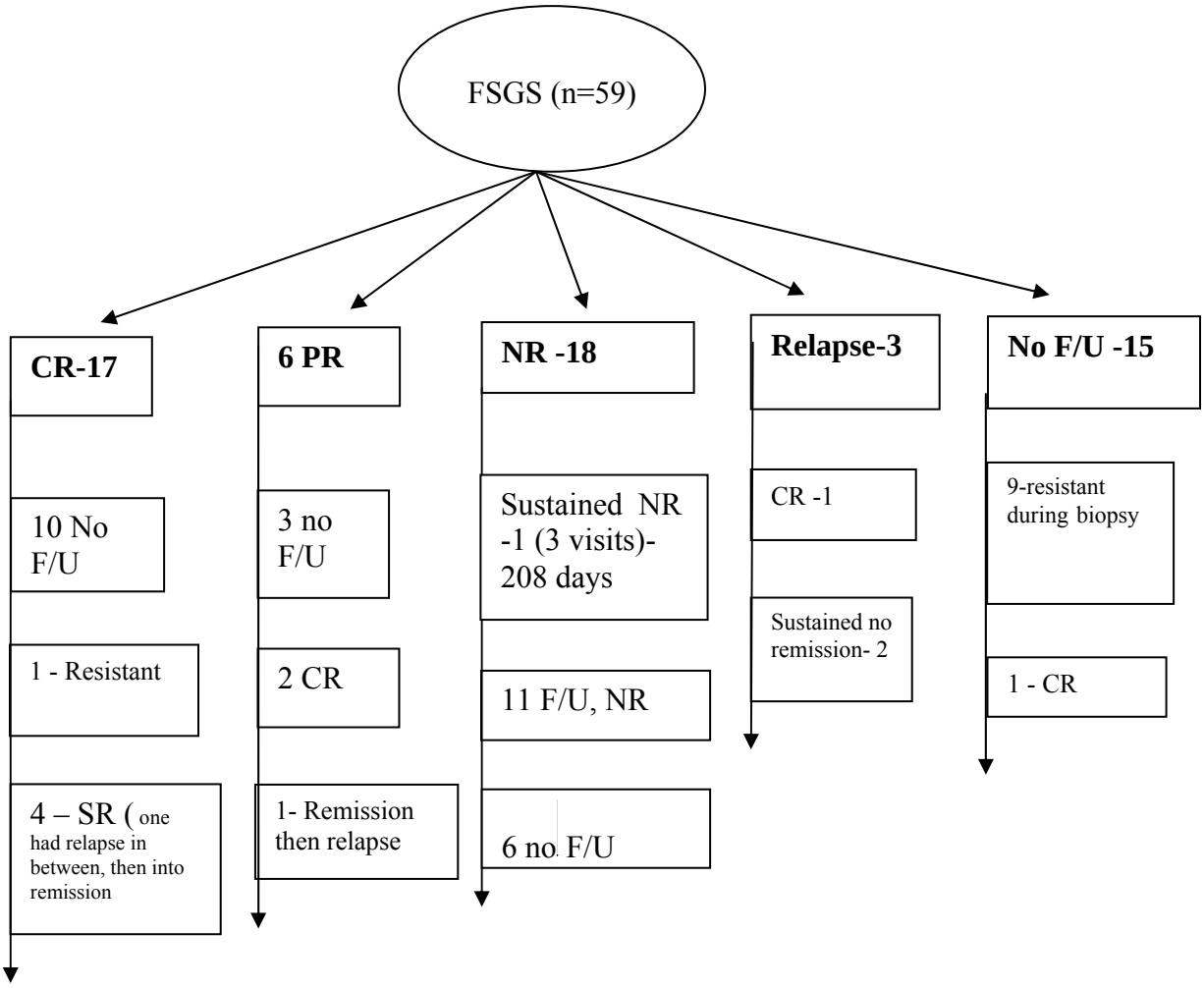
Focal Segmental Glomerulosclerosis(FSGS) (n = 59)	Characteristics
Gender (M:F)	2.2 :1
Age (Mean ± SD, Range)	11.6 ± 5.4, 1.2 – 18
Nephrotic: Subnephrotic	44:11(valid 55)
Time for remission (Median days, range)	167, 15 – 1295
Follow up in days (Median Range)	562.5. 15 – 2200
Creatinine (Mean ± SD, Range)	1.28 ± 1.2, 0.3 – 6.8 mg%
24 Hr Urine protein (Median, Range)	4200, 64mg – 17.0 gm
Serum albumin (Mean ± SD, Range)	2.1 ± 1.12, 0.67 – 4.3gm
Hypercholesterolemia	28(77.8%) valid for 36 pt only

Males were predominant in this group (M: F = 2.2:1). The mean age was 11.6 ± 5.4 years (range: 1.2 – 18). Mean creatinine value was 1.28 ± 1.2 mg% (range:0.3 -6.8),mean serum albumin was 2.1 ± 1.12, 0.67 – 4.3 gm whereas median 24 hour median urinary protein was 4200 mg (mean: 64 mg – 17.0 gm). The median days of follow up was 562 days (range: 15 -2200) and the median time for remission was 167 days (range: 15 -1295).

Table 11: Treatment received (prior to coming to CMC vellore)

Drug	Frequency	Percent (%)
No Treatment	9	15.3
Prednisolone	47	79.7
Pred nisolone + Cyclophosphamide	1	1.7
Prednisolone + Cyclosporine	1	1.7
ACE Inhibitor	1	1. 7
Total	**59**	**100.0**

Figure 7: Outcome of patients with focal segmental glomerulonephritis (FSGS)



CR – Complete remission ; PR – Partial remission ; SR – Sustained remission; SPR – Sustained partial remission ; NR – No remission; No F/U – No follow up.

Figure 7 Shows the outcome of patients with focal segmental glomerulonephritis (FSGS). Out of 59 patients with FSGS, 17(28.81%) patients achieved complete remission, 6(10.16%) patients achieved partial remission,3 patients had relapse , 18 (30. 50%) did not achieve remission, 15 (25.42%) lost follow up after biopsy.

Among the complete remission group 13(76.47%) patients were treated with only steroid.

1 (5.88%) patient was treated with combination of steroid & cyclosporine, 3(17.64%) patients were treated with combination of steroid & cyclophosphamide. 6 (10.16%) patients were in partial response only treated with steroid. Among the resistant group 14 (77.77%) were treated with steroid,1 patient was on combination of steroid & cyclosporine, 2 patients were treated with steroid & cyclophosphamide, 1 patient was treated with combination of steroid & mycophenolate.

Table 12: Characteristics of patients with IgA nephropathy

IgA Nephropathy(IgAN) (n =61)	Characteristics
Gender (M:F)	1.4 : 1
Age (Mean ± SD, Range)	14.6 ± 3.3, 4 – 18
Nephrotic: Subnephrotic	28:30 (valid 58)
Time for remission (Median days, range)	147, 71 - 3107
Follow up in days (Median Range)	567, 86 - 3522
Creatinine (Mean ± SD, Range)	1.59 ± 0.23, 0.4 – 8.8 mg%
24 Hr Urine protein (Median, Range)	1200, 17mg – 11.1gm
Serum albumin (Mean ± SD, Range)	3.3 ± 0.95, 1.2 – 4.9 gm
Hypercholesterolemia	19 (65.5%) valid for 29 pt only

Table 12 shows the characteristics of 61 patients with IgA nephropathy . Males were predominant in this group (M: F = 1.4:1). The mean age was 14.6 ± 3.3 years (range: 4 – 18). Mean creatinine value was 1.59 ± 0.23 mg% (range:0.4 -8.8) whereas median 24 hour urinary protein was 1200 mg (mean: 17 mg – 11.1 gm). The median days of follow up was 567 days (range: 86 -3522) and the median time for remission was 147 days (range: 71 -3107).

Table 13: Treatment received (prior to coming to CMC vellore)

Drug	Frequency	Percent (%)
No Treatment	37	60.7
Prednisolone	21	34.4
Anti hypertensives	1	1.6
ACE Inhibitors	1	1.6
Native medication	1	1.6
Total	**61**	**100**

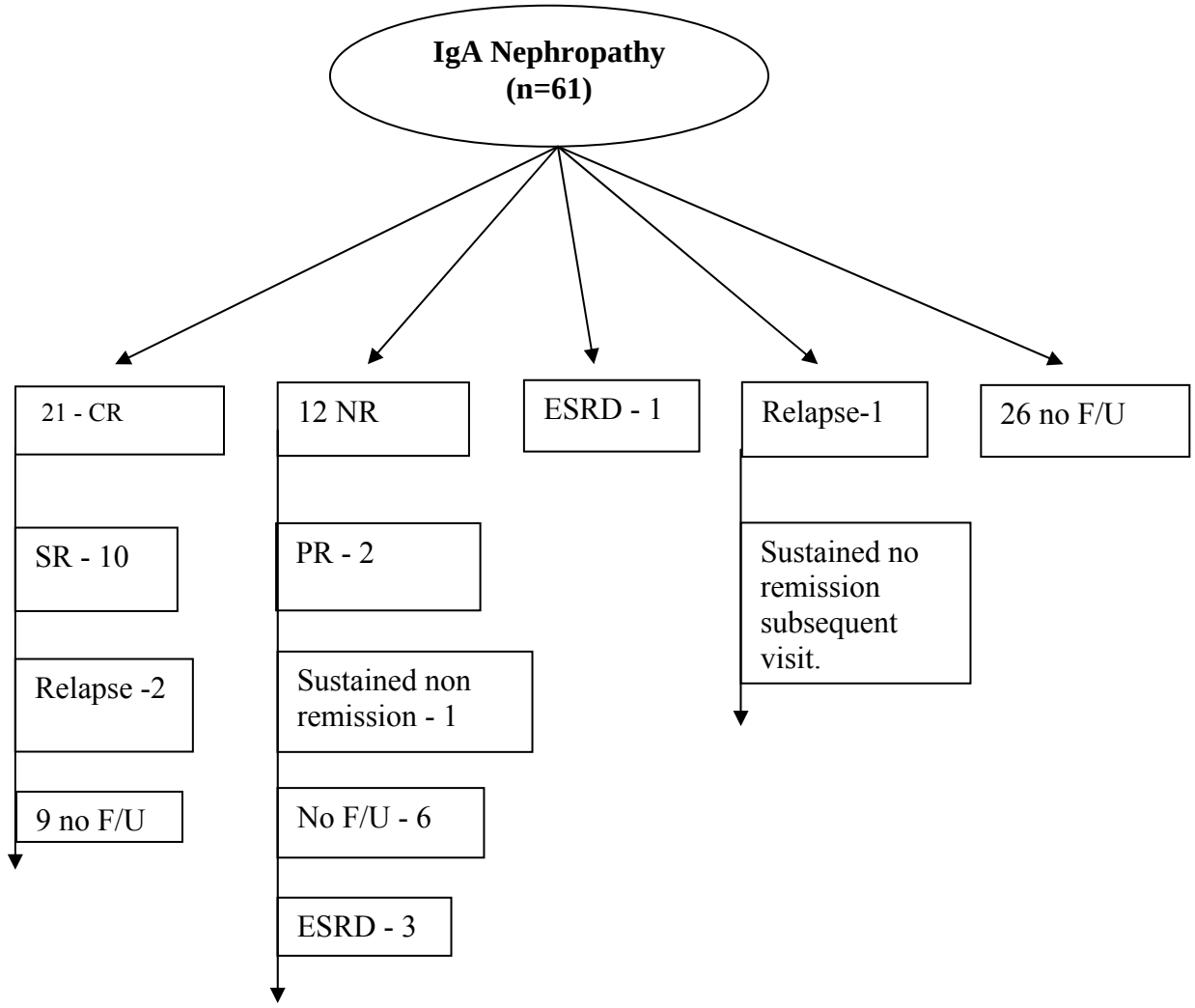
Table 13 shows total of 61 patients of IgA nephropathy prior to coming to us 21 were treated, (34.4%) were treated with prednisolone. One patient each was treated with antihypertensive drug, ACE inhibitor and native medications. 37 (60.7%) patients did not receive any treatment.

Table 14 : Histologic picture in patients with IgA nephropathy.

	Frequency	Percent
IgA Nephropathy	41	67.2
IgA nephropathy + Crescents	7	11.5
HSP	5	8.2
End Stage IgA	8	13.1
Total	**61**	**100**

Table 14 shows the characteristic histologic picture by light microscopy in patients with IgA nephropathy. Out of a total of 61 cases, features of only IgA nephropathy was seen in 41 (67%) of patients; IgA nephropathy with crescents were seen in 7(11.5%) patients whereas end stage IgA nephropathy was seen in 8(13%) of cases.

Figure – 8: Outcome of patients with IgA nephropathy



CR – Complete remission ; PR – Partial remission ; SR – Sustained remission; SPR – Sustained partial remission ; NR – No remission; No F/U – No follow up.

Figure 8 shows the outcome of IgA patients. Out of 61 patients with IgA nephropathy, 21 (34.42%) patients achieved complete remission,12 (19.67%) patients did not achieve remission.1(1.6%) patient had relapse, 4 (6.55%) patient went into end stage renal disease.26 (42.62%) patient lost follow up.

Table 15: Characteristics of patients with Mesangial proliferative glomerulonephritis .

Mesangio Proliferative GN (n =146)	Characteristics
Gender (M:F)	2.1 : 1
Age (Mean ± SD, Range)	12.4 ± 4.5, 2- 18
Nephrotic: Subnephrotic	100:33 (valid for 133 pts)
Time for remission (Median days, range)	189, 28 – 3302
Follow up in days (Median Range)	425, 28 – 3302
Creatinine (Mean ± SD, Range)	0.89 ± 0.79, 0.2 – 6.7 mg%
24 Hr Urine protein (Median, Range)	1.8gm, 12 mg – 20.0gm
Serum albumin (Mean ± SD, Range)	2.8 ± 1.16, 0.9 – 4.9gm
Hypercholesterolemia	63 (43.2%) valid for 84 pt only

Table 15 shows the distribution of Mesangio proliferative glomerulonephritis . The total number of patients was 146. Mean age was 12.4 ± 4.5, 2 - 18 years and it showed male preponderance. Mean creatinine was 0.89 ± 0.79, 0.2 – 6.7 mg%, mean serum albumin was 2.8 ± 1.16, 0.9 – 4.9 gm whereas median 24 hour mean urinary protein was 1.8 gm (range :12 mg – 20 gm). The median days of follow up was 425 days (range: 28 -3302) and the median time for remission was 189 days (range: 28 -3302)

Table 16: Histological types of Mesangial proliferative GN.

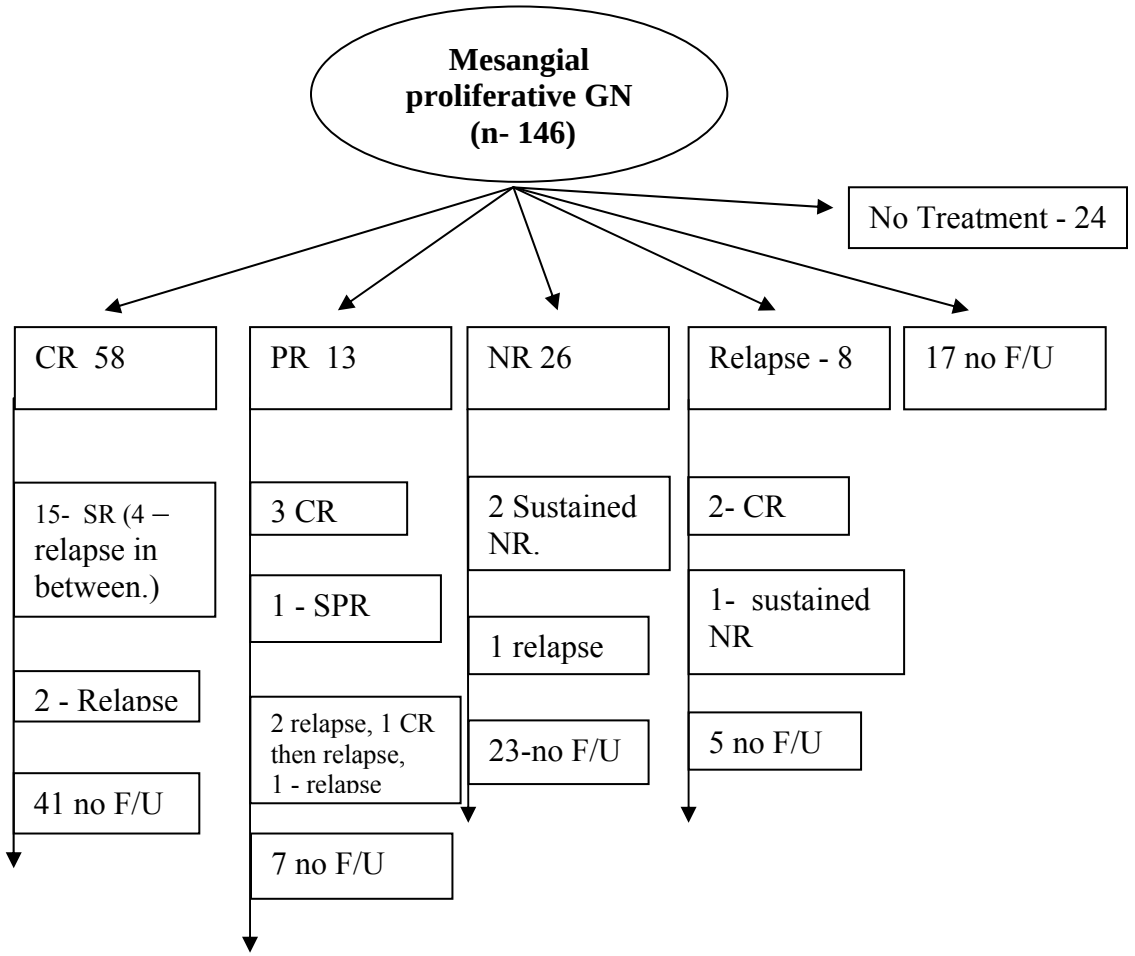
LM Biopsy proven (n = 146)	Frequency	Percent %
Mesangial proliferative GN	100	68.5
Mesangial proliferativ GN + Fibrous crescents	2	1.4
Mesangial proliferativ GN + Segments of Sclerosis	24	16.4
Mesangial proliferative GN with glom hyalinization	1	0.7
Mesangial proliferative GN + Segmental & global glomerulosclerosis	1	0.7
Diffuse mesangial proliferative GN	3	2.1
Mesangial Prol. GN with resolving PIGN	14	9.6
Mesangial proliferaive GN with Interstitial foarm cells	1	0.7
Total	**146**	**100**

Table 16 shows the various histological types of Mesangial proliferative GN. Only mesangial proliferative features were seen in the maximum (68.5%) cases whereas Mesangial proliferation with segments of sclerosis were seen in 16% cases. Mesangial proliferation with resolving PIGN was seen in about 10% cases.

Table 17. Treatment received (prior to coming to CMC vellore)

Drug	Frequency	Percent (%)
No Treatment	57	39
Prednisolone	85	58.2
Pred + Endoxan	3	2.1
Pred + MMF	1	0.7
Total	**146**	**100**

Figure-9: Out come of patients with Mesangial proliferative GN



CR – Complete remission ; PR – Partial remission ; SR – Sustained remission; SPR – Sustained partial remission ; NR – No remission; No F/U – No follow up.

Figure 9 shows out come of patients with Mesangial proliferative GN.

Among 146 patients 58 (39.72%) achieved complete remission ,13 (8.90%) patients achieved partial remission, 8 (5.47%) patients had relapse, 26 (17.80%) patients did not achieve remission.17 (11.64%) patients lost follow up, 24 (16.43%) patients did not receive any treatment.

Among the complete remission group 37 (63.79%) patient were treated with only steroid. 2 (3.44%) patients were treated with only levamisole, 2 (3.44%) patients were treated with combination of steroid and cyclosporine,14(24.13%) patients were treated with combination of steroid & cyclophosphamide, 1(1.72%) patient was treated with combination of steroid with azathioprine,2(3.44%) patients were treated with combination of steroid and levamisole.

Among 13 patients who had partial remission 12 (92.30%) of them were treated with steroid and 1(7.69%) had received combination of steroid and levamisole.

Among the 26 patients who did not achieve remission, 17 (65.38%) patients were treated with steroid, 3 (11.53%) were treated with mycophenolate, 1(3.84%) patient was treated with levamisole,3 (11.53%) patients were treated with combination of steroid and cyclosporine,

1(3.84%)patient was on combination of steroid and azathioprine,1 ((3.84%) patient was treated with combination of steroid and mycophenolate.

Table: 18 Characteristics of patients with Lupus Nephritis (LN)

Lupus Nephritis (n=98)	Characteristics
Gender (M:F)	1: 6.4
Age (Mean ± SD, Range)	15.37 ± 2.5, 8.5 -18
Nephrotic: Subnephrotic	50:39 (valid: 89/98)
Time for remission (Median days, range)	209,21 – 3209
Follow up in days (Median Range)	905, 21 – 3209
Creatinine (Mean ± SD, Range)	1.5 ± 0.20, 0.4 – 15.6mg%
24 Hr Urine protein (Median, Range)	0.8gm, 24 mg – 1.6 gm
Serum albumin (Mean ± SD, Range)	2.7 ± 0.9, 0.4 – 4.6gm
Hypercholesterolemia	23(23.5%) valid for 29 pt only
Antinuclear antibody positive	79 (80.6%)
Comlement level C3 low (<90)	39 pt (valid for 41 pt), 95.1%
Comlement level C4 low (10)	25 pt(valid for 41 pt), 61.0%
Anti DS DNA antibody	Elevated in 48 pt (valid upto 68pt),70.6% 20 pt (29.4%) DsDNA Normal.(< 30)

Table 18 shows the characteristics of 98 patients with LN . Females were predominant in this group (M: F = 1:6.4). The mean age was 15.37 ± 2.5, 8.5 - 18 (range: 8.5 – 18). Mean creatinine was 1.5 ± 0.20, 0.4 – 15.6 mg%, whereas median 24 hour urinary protein was 0.8 gm (mean: 24 mg – 1.6 gm),Mean serum albumin 2.7 ± 0.9, 0.4 – 4.6 gm. The median days of follow up was 905 days (range: 21 -3209) and the median days for remission was 209 days (range: 21 -2256).

Table 19.Various classes of Lupus nephritis.

WHO classes of LN	Frequency	Percent (%)
Class I	1	1.0
Class II	17	17.3
Class III	8	8.2
Class IV	66	67.4
Class V	6	6.1
Total	**98**	**100**

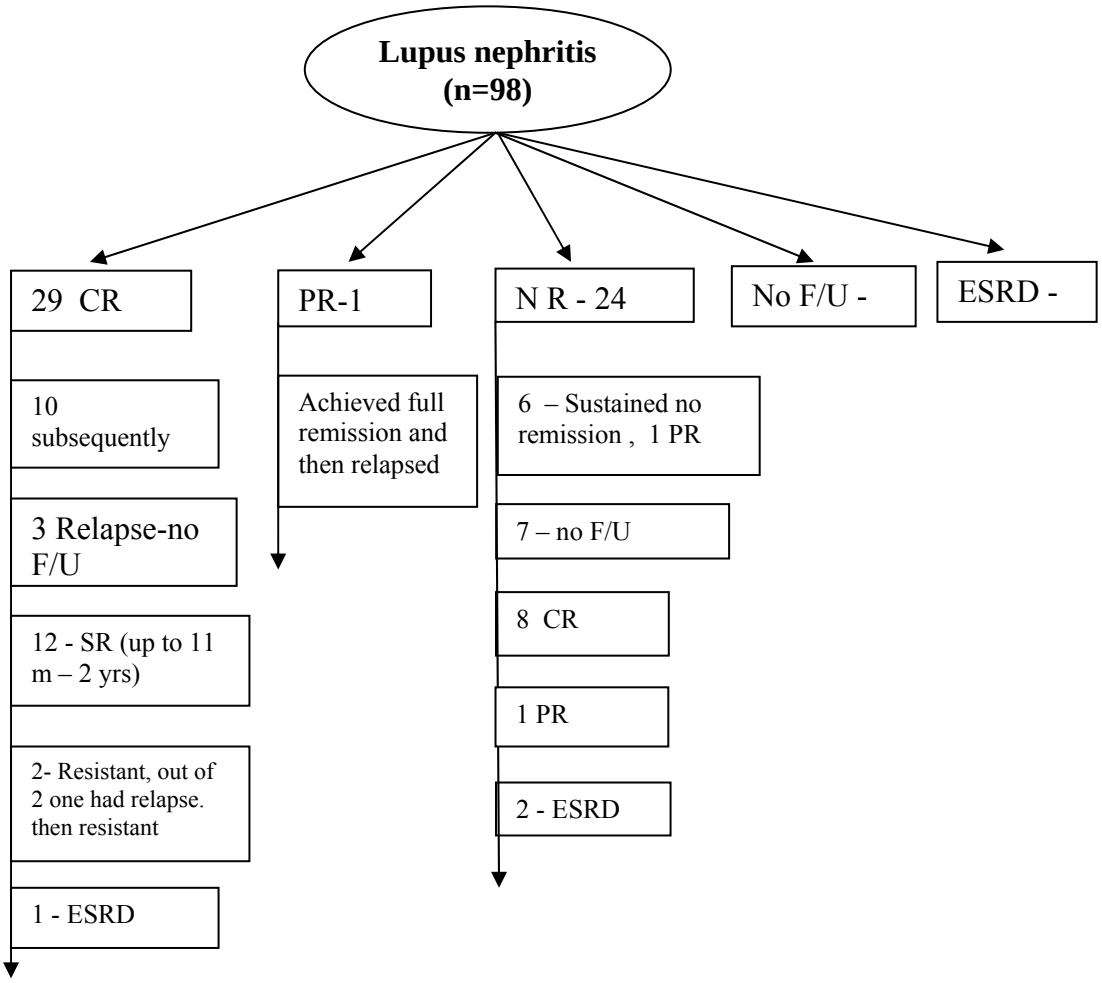
Table 19 shows based on the initial biopsies the various histological classes of patients with Lupus nephritis were 66 (67.4%) patients had class IV LN and it constituted the largest group. Class II was the second largest group 17(17.3%) cases whereas class III, class V and class I constituted 8(8.2%) , 6(6.1%) and 1 (1.0% respectively.

Table - 20: Treatment received (prior to coming to CMC vellore)

Drug	**Frequency**	**Percent**
No Treatment	13	13.4
Prednisolone	79	80.4
Prednisolone + Cyclophosphamide	2	2.1
Prednisolone + IV Cyclophosphamide	1	1.0
Azathioprine	1	1.0
Immunoglobulin	1	1.0
Prednisolone + Cyclophosphamide + Azathioprine + Cyclosporine	1	1.0
Total	**98**	**100**

Table 20 : shows the distribution of patients who had been treated with different drugs before presenting to us. Out of 98 cases, 78 (79.6%) patients were treated with prednisolone and this constituted the largest group. Two (2%) patients had received prednisolone and cyclophosphamide whereas 13 (13%) patients had not received any treatment before presenting to us.

Figure 10: Outcome of patients with Lupus Nephritis.



CR – Complete remission ; PR – Partial remission ; SR – Sustained remission; SPR – Sustained partial remission ; NR – No remission; No F/U – No follow up.

Figure 10 shows Outcome of 98 patients with Lupus Nephritis. Complete remission was achieved in 29 cases (12 – sustained remission, 3 relapses) whereas 1 patient had partial remission .24 patients did not achieve remission. 42 patients lost follow up after first revisit. On final follow up 5 children approached end stage renal disease.

The various classes of lupus nephritis were treated with various immunosuppression medications.

Among the 29 children who went into complete remission, class IV LN 18(62.06%),class III LN 4 (13.79%),class II LN 4 (13.79%),class V LN 3 (10.34%),non of them were class I . Among the 18 children with class IV LN, 2 received only prednisolone,10 received combination of prednisolone and Azathioprine,5 received combination of prednisolone and cyclophosphamide,1 child received combination of prednisolone and mycophenolate. Of the 4 children with class III LN who went into remission 3 children were treated with combination of prednisolone and Azathioprine , 1 child was treated with combination of prednisolone and mycophenolate. Of the 4 children with class II LN who went into remission all were treated with combination of prednisolone and Azathioprine. There were 3 children in class V LN who achieved remission 2 were treated with combination of prednisolone and Azathioprine and 1 was treated with combination of prednisolone and cyclosporine.

Table 21: Characteristics of patients with Acute Proliferative Glomerulonephritis

Proliferative Glomerulonephritis (n=81)	Characteristics
Gender (M:F)	1.6:1
Age (Mean ± SD, Range)	13.4 ± 3.9, 1 – 18
Nephrotic: Subnephrotic	46:30 (valid:76/81)
Time for remission (Median days, range)	152, 16 – 2125
Follow up in days (Median Range)	252, 16 – 2910
Creatinine (Mean ± SD, Range)	2.0 ±0.37, 0.4 – 25.0mg%
24 Hr Urine protein (Median, Range)	2.2gm, 34 mg – 12.7gm
Serum albumin (Mean ± SD, Range)	2.73 ± 1.03, 0.2 – 4.5gm
Hypercholesterolemia	224(29.6%) valid for 34 pt only

Table 21 shows the characteristics of 81 patients with Proliferative Glomerulonephritis . Males were predominant in this group (M: F = 1.6:1). The mean age was 13.4 ± 3.9 years (range:1- 18).

Mean creatinine was 2.0 ± 0.37 mg%, (range:0.4 -25 mg%),mean serum albumin was 2.73 ± 1.03,(range : 0.2 – 4.5 gm) whereas median 24 hour mean urinary protein was 2.2 gm (range : 34 mg – 12.7 gm). The median days of follow up was 252 days (range: 16 -2910) and the median days of remission was 152 days (range: 16 -2125).

Table : 22, Various histological finding in Proliferative GN

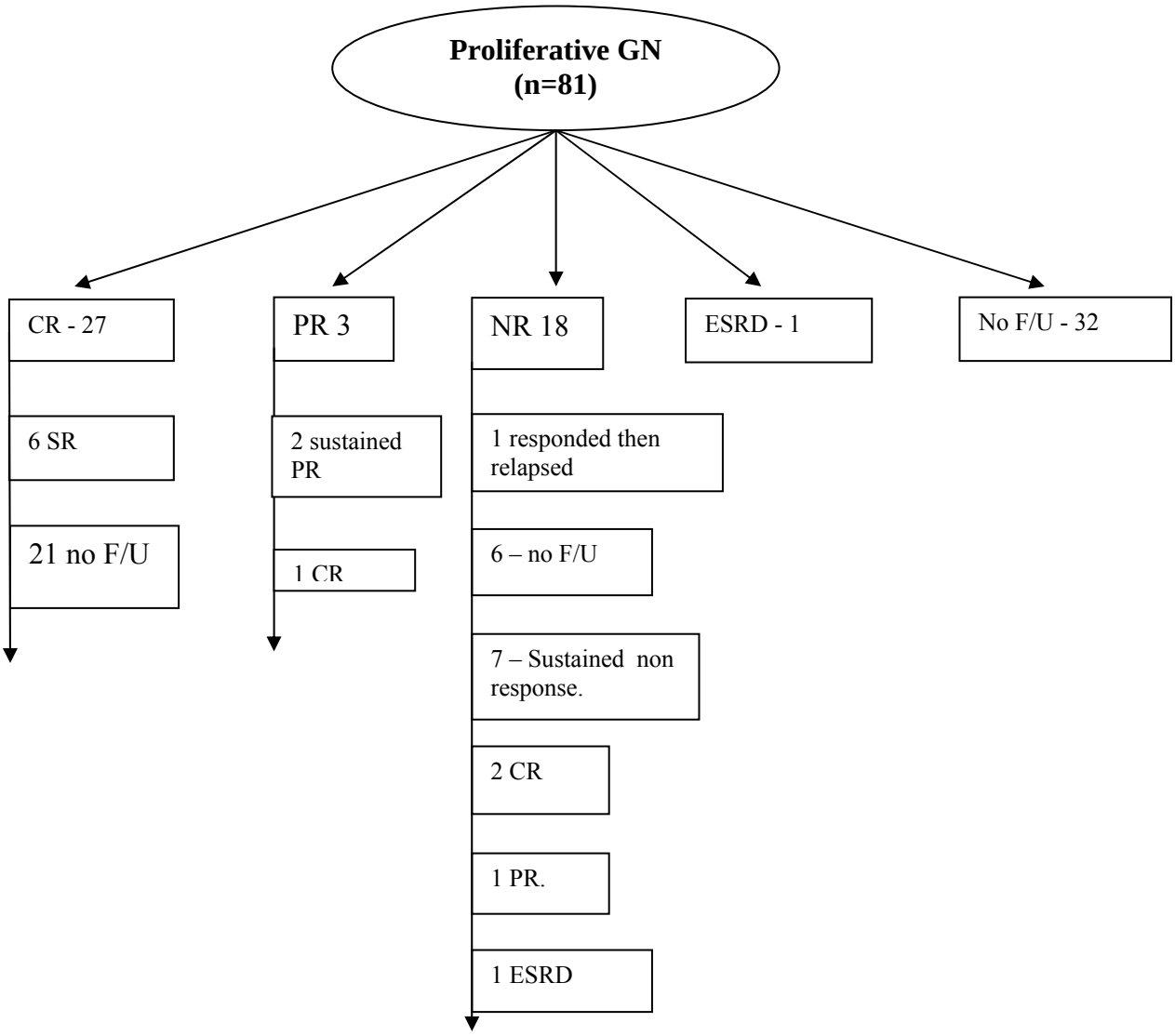
	Frequency	**Percent (%)**
Proliferative GN	1	1.2
Focal proliferative GN	1	1.2
Focal segmental proliferative GN	8	9.9
FS proliferative GN with fibrocellular crescents	1	1.2
Focal proliferative and sclerosing GN	3	3.7
Acute proliferative GN	4	4.9
Diffuse proliferative GN	3	3.7
Diffuse endo capillary exudative proliferative GN	47	58.0
DPGN + cellular crescents	4	4.9
DPGN + Fibrocellular crescents	5	6.2
DPGN + Segmental capillary wall thickening	3	3.7
End stage proliferative and sclerosing GN	1	1.2
Total	**81**	**100**

Table 22 shows, Diffuse endocapillary and proliferative glomerulonephritis constituted the largest group and it was seen in 47 (58%) cases. Focal segmental proliferative GN was seen in 8 (9.9%) cases.

Table 23 Treatment received prior to coming to CMC vellore

	Frequency	**Percent**
No Treatment	53	65.4
Prednisolone.	26	32.1
Anti hypertensives	2	2.5
Total	81	100

Figure – 11: Outcome of patients with Proliferative Glomerulonephritis.



CR – Complete remission ; PR – Partial remission ; SR – Sustained remission; SPR – Sustained partial remission ; NR – No remission; No F/U – No follow up.

Figure 11: shows the status of 81 patients with Proliferative Glomerulonephritis. 27 (33.33%) patients achieved complete remission, 3(3.70%) patients achieved partial remission,18 (22.22%) patients did not achieve remission, 1(1.23%) patient developed end stage renal disease. 32 (39.50%) patients lost follow up.

Out of 27 patients who were in complete remission 20 (74.04%) were treated with only steroid , 1(3.70%) patient was on combination of steroid and cyclosporine, rest 6 (22.22%)were not given any treatment.18 patients did not achieve remission, 16(88.88%) of them were treated with steroid only.Rest 2 were treated with combination of steroid and mycophenolate & steroid and azathioprine.

Table - 24 : Characteristics of patients with Crescentic glomerulonephritis

Crescentic glomerulonephritis (n=15)	Characteristics
Gender (M:F)	1:4
Age (Mean ± SD, Range)	14.83 ± 4.09, 4 – 18
Nephrotic: Subnephrotic	8 (80%) : 2 (20%) valid for 10 patients only
Time for remission (Median days, range)	206.5 (26 – 762)
Follow up in days (Median Range)	206.5 (26 – 762)
Creatinine (Mean ± SD, Range)	5.62 ± 2.85 , 1.2 – 11.6mg%
24 Hr Urine protein (Median, Range)	4.6gm, 0.749 mg – 8.6gm
Serum albumin (Mean ± SD, Range)	2.12 ± 0.73, 0.73– 2.7gm
Hypercholesterolemia	2 (valid for 2 pt only)

Table - 24 shows the characteristics of 15 (1.69%) patients with Crescentic glomerulonephritis

Membranous glomerulonephropathy accounted for 24(2.70%) ,13 out of 24 were in remission during the first revisit,10 of them were treated with combination of steroid and cyclophosphamide,3 were treated with only steroid.

Membrano proliferative glomerulonephritis contributed to 8(0.9 %).

Electron microscopy examination reports were available for 14 pts(1.6%). Among them 9(1%) Alports syndrome , MPGN was 0.1%, only mild foot process effacement was seen in 3% and Inconclusive reports in 0.1% case.

DISCUSSION

The underlying histopathological characteristics in nephrotic syndrome are of immense significance in determining steroid responsiveness and long-term prognosis.

Several studies have reported on the relative distributions of various diagnostic categories in large series of paediatric renal biopsies. As there may be differences in the protocol or indication for biopsy across centers or countries, the results may not be directly comparable, but they do provide an overview of the most commonly encountered entities.

In the study reported by **ISKDC**[14] on renal biopsies done for 521 children, the distribution of various histological diagnosis were as follows: Minimal change nephrotic syndrome 398 (76.4%), Membranoproliferative glomerulonephritis 39(7.5%), Focal & segmental glomerulosclerosis 36(6.9%), Proliferative glomerulonephritis 12(2.3%), Pure diffuse mesangial proliferation 12 (2.3%), Focal & global glomerulosclerosis 9(1.7%), Membranous glomerulonephropathy 8(1.5%), Chronic glomerulonephritis 3(0.6%), Unclassified 4 (0.8%).

In the **Italian National Registry** of renal biopsies in children, the distributions of **t**he most common glomerular diseases were, in order of frequency, IgA nephropathy, Henoch–Scho¨nlein nephritis, minimal-change disease (MCD), focal segmental glomerulosclerosis (FSGS), mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, lupus nephritis and TGBM disease/Alport syndrome. In this series, the indication for renal biopsy was isolated microscopic haematuria in 20% of cases, non-nephrotic proteinuria with or without microscopic haematuria in 30%, nephrotic-range proteinuria in 35% and acute or chronic renal failure in 15%[61].

The largest single study reported on more than 1700 paediatric renal biopsies from a **Korean registry**, in which the most common primary glomerular conditions were MCD (25%), IgA nephropathy (10%), acute post-infectious glomerulonephritis (9%), and FSGS (4%), with Henoch–Scho¨nlein and lupus nephritis as the most common secondary conditions[62].

Similarly, the study published from the **Czech registry** on 709 biopsies in children, reported the most common diagnoses in children to be IgA nephropathy (19%), MCD (18%) and TGBM nephropathy (12.3%)[63].

In another series of 322 children specifically presenting with haematuria, the frequencies of various diseases were IgA nephropathy in 24%, Alport nephropathy in 27%, TGBM nephropathy in 16%, other glomerulopathy in 19% and normal glomeruli in the remaining 15%[64].

In a study from India, in 250 children with pure nephrotic syndrome, Minimal Change Disease comprised more than half of the cases[65].

In another report from Great Ormond Street Hospital, from an unselected series of more than 1250 consecutive paediatric renal biopsies for all non-tumour indications has demonstrated a range of histological findings out of which MCD, IgA nephropathy and Henoch–Scho¨nlein nephritis represent the most common entities[66].

In two other studies including more than 300 children biopsied for steroid-resistant or atypical nephrotic syndrome from India, FSGS was diagnosed in 40%, followed by minimal-change nephropathy in 20–30%, Membranoproliferative GN in 15%, mesangial proliferative in 10% and membranous in 5% children. In younger children, however, MCD was the most common entity, whereas FSGS predominated in the older children[41, 67].

A study done from India has shown the analysis of 910 renal biopsy in which the the commonest indication for renal biopsy was nephrotic syndrome.The histopathological diagnoses were as follows,diffuse mesangioproliferative glomerulonephritis as commonest 36%, minimal change disease 24.75%,focal segmental glomerulosclerosis 11.5%, IgM 1.3%, and IgA nephropathy 1.2%,systemic vasculitis 2.5%[68].

A study done from our centre has shown the histopathological reports of all native kidney biopsies performed from 1990 – 2001. Total number of biopsies were 5258 out of which 928 were children (<15 years). The various histological diseases were MCD in 47.2%.

FSGS in 12.5%**,** mesangial PGN in 11.3%, endocapillary proliferative GN in 8.8% and lupus nephritis in 3.5% children[69]. The incidence of MPGN had declined to 2.6% in this study when compared to 7.2% between 1970 and 1985.

In the present study, the distribution of various diseases were as follows: Minimal change disease in 303 (34.16%), Mesangial proliferative GN in 146 (16.45%), Lupus nephritis in 98(11.05%), Proliferative glomerulonephritis in 81(9.13%), IgA nephropathy in 61 (6.87%), Focal segmental glomerulosclerosis in 59(6.65%), Diffuse mesangial hypercellularity in 53(5.97%), Membranous glomerulonephropathy in 24(2.70%), Crescentic glomerulonephritis in 15(1.69%), Membrano proliferative glomerulonephritis in 8(0.9 %),Hemolytic uremic syndrome in 5 (0.56 %),Vasculitis in 3(0.33 %), acute interstitial nephritis in 3(0.33 %), acute tubular necrosis in 2(0.22 %), granulomatous interstitial nephritis in 3(0.33%), end stage etiology of unknown etiology in 17(1.92 %) and inadequate sample in 2 (0.22%) children. It appears that the incidence of Lupus nephritis is higher in our patients in comparison to other study published in literature[69]. The same also has been shown in another study [70] done on lupus nephritis in paediatric population.

In the study published by ISKDC[14], the number of children with less than or equal to 6 years of age with a histological diagnosis of MCD, FSGS and MPGN were 79.6%, 50% and 2.6% respectively. In this study, the respective percentages in MCD and FSGS are 43.9%, 25.4%. None of the children with MPGN were below 6 yrs of age. In a study published in children with lupus nephritis[70], the median age was 13.7 years and female:male ratio was 5.5:1 and in our study patients with lupus nephritis, the median age was 15.3 years and female :male ratio was 6.4 : 1.

Hypertension was seen in 20.7 % patients with MCD, 48.5 % patients with FSGS and 51.4% patients with MPGN in the study published by ISKDC[14]. In our patients, hypertension was seen in 7% patients with MCD, 21.1%patients with FSGS and 12.1 % patients with MPGN. Hypertension was seen in 59% of children with lupus nephritis[70]. Hypertension was seen in 19.6% of patients with lupus nephritis in our patients. Hypertension was seen in 15.7% children with mesangioproliferative GN and 8.2% of children with IgA nephropathy.

Similarly, haematuria was seen in 22.7% patients with MCD, 48.4% patients with FSGS and 58.8% patients with MPGN in the study published by ISKDC[14] . In our patients, haematuria was seen in 9% patients with MCD, 12.8% patients with FSGS and 28.6% patients with MPGN. Haematuria was seen in 31.7 % children with mesangioproliferative GN, 46.5% of children with IgA nephropathy and 13.7% of children with lupus nephritis.

In the study published by ISKDC[71] in 389 children with MCD, 92% children responded to steroid and out of them 41% had a sustained remission whereas, 48% of children either had a single or multiple relapse. In this study, among the 303 patients with MCD, 70% responded to steroid and out of them, 33% had sustained remission on long term follow up.

In patients with lupus nephritis, the initial response to steroid either alone or combination with other immunosuppressive drugs has been shown to be 87% in a study published from South Korea[72]. However, in this study the response in lupus nephritis has been found to be 53%.

In patients with FSGS, the complete response to steroid was seen in 38% children and steroid resistant was seen in 29% of children in a recent study published from Brazil[73]. In our patients with FSGS, the complete response to steroid was seen in 32% of children whereas 30% of children were found to be resistant to steroid.

Conclusion:

Among the children, who present with nephrotic syndrome, Minimal Change Disease (MCD) is found to be the commonest histopathological diagnosis in children under 8 years of age. The incidence of MPGN has declined in this study and a similar trend has been shown in other studies as well. The response of children with MCD to corticosteroid is comparable to that available in literature. The incidence of lupus nephritis has been found to be increased in this study; however the response to steroid is found to be less in comparison to literature. The response of children with FSGS to steroid is similar to that published in literature.

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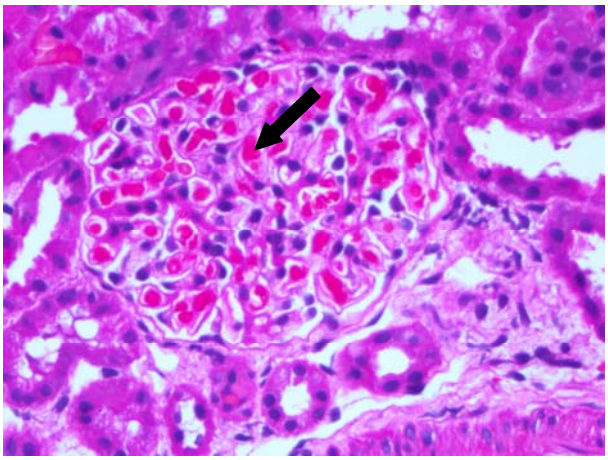
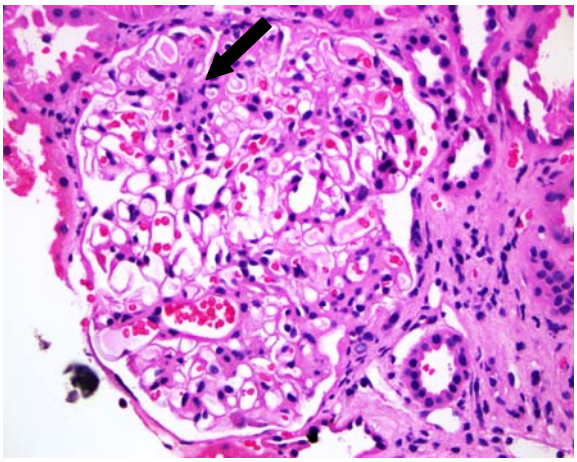
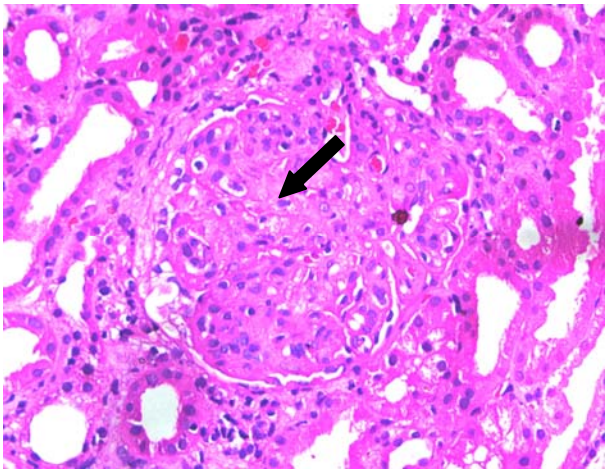


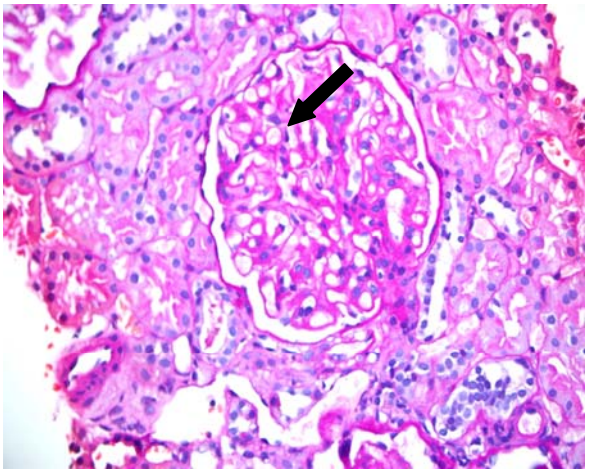
Picture 1. Minimal Change Disease. Arrow points to normal mesangial cellularity. H &E stain, magnification 40x.



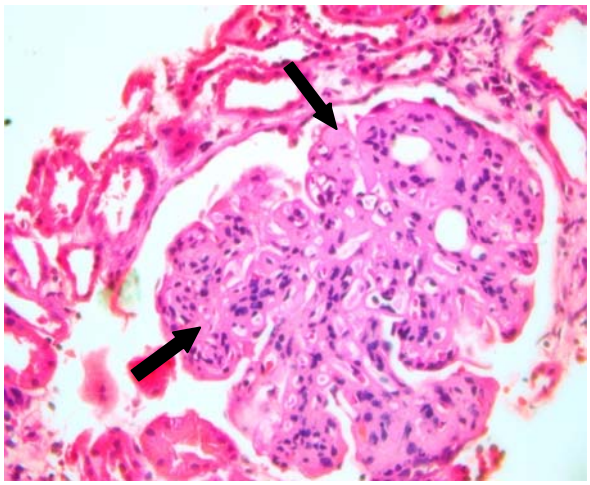
Picture 2 Mesangial Proliferative GN. Arrow points to mesangial proliferation H &E stain, magnification 40x.



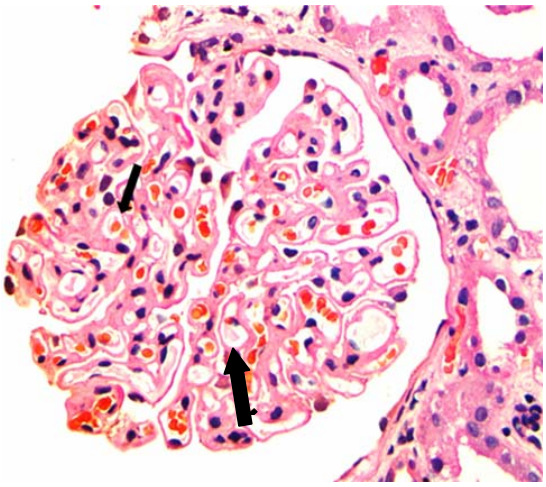
Picture 3 Diffuse proliferative GN. Arrow points to diffuse proliferation of the Mesangial cells & endocapillary cells. H &E stain, magnification 40x. .



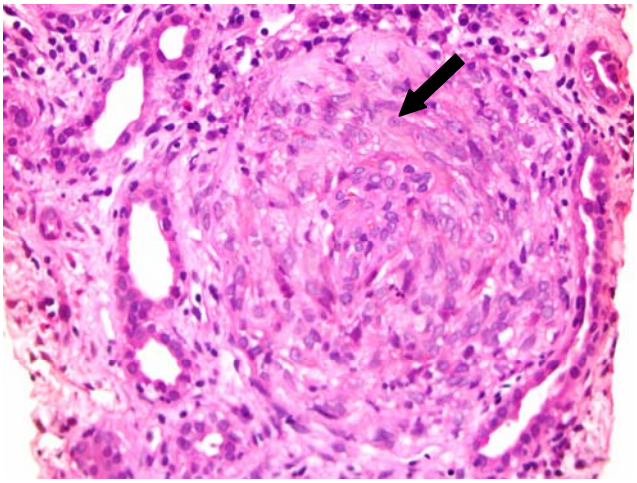
Picture 4 Membranous nephropathy Arrow points uniform increased capillary wall thickening. H &E stain, magnification 40x.



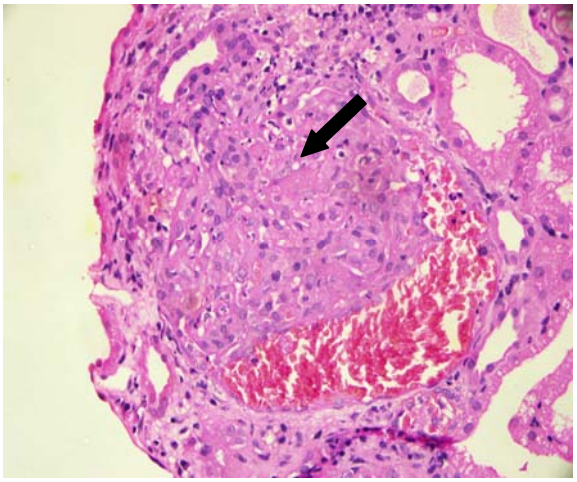
Picture-5 Membranoproliferative GN. Arrow points to increase lobultion, intracapillary hypercellularity and thickening of capillary wall.
H &E stain, magnification 40x.



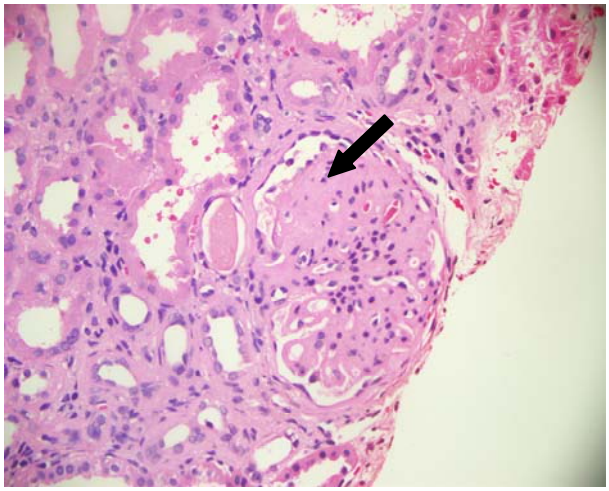
Picture-6 Advanced Membranous . nephropathy. Arrow points uniform thickening of capillary wall.
H &E stain, magnification 40x.



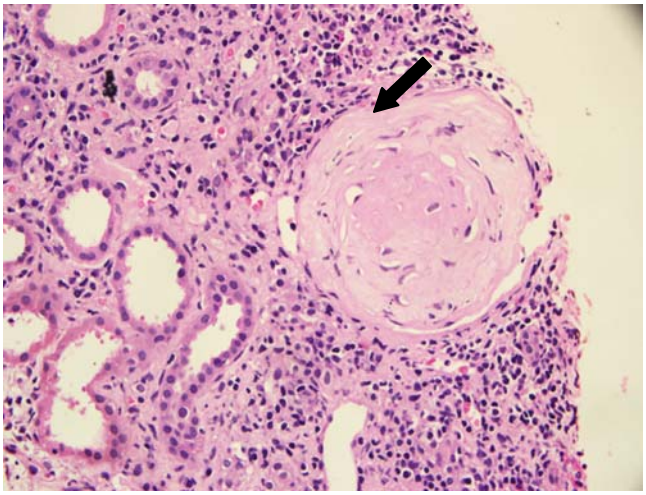
Picture 7 Crescentic GN.
Arrow points to circumferential cellular crescent . H &E stain, magnification 40x.



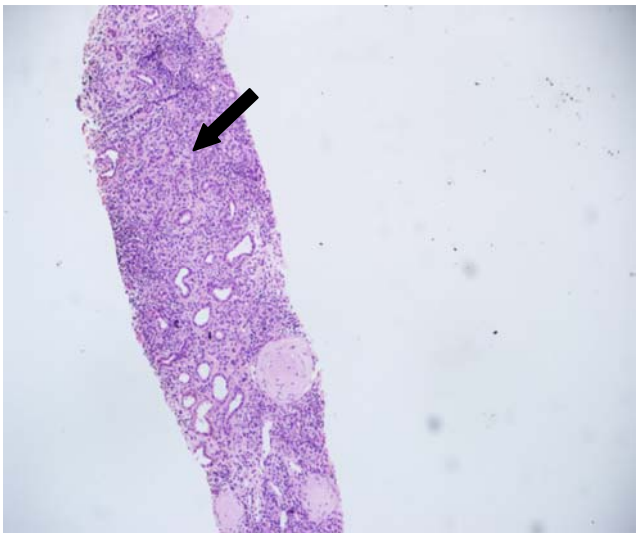
Picture 8 Vasculitis. Arrow points necrotizing and crescentic GN.
H &E stain, magnification 40x.



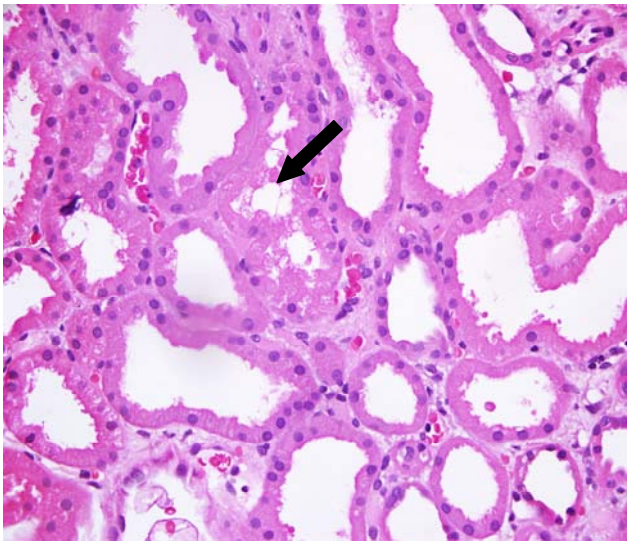
Picture 9 Focal segmental glomerulosclerosis.
Arrow shows segmental sclerosis.
H &E stain, magnification 40x



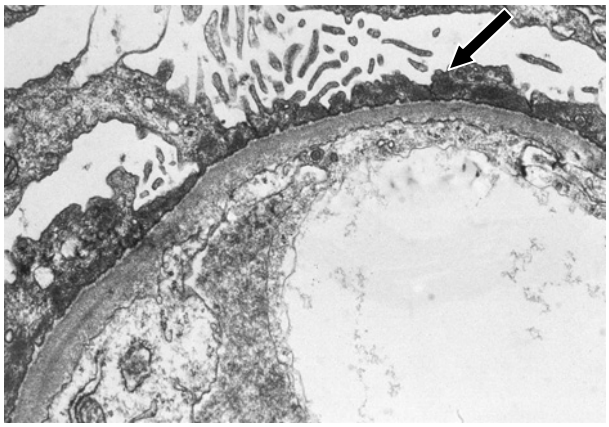
Picture 10 End stage histology.
Arrow shows global glomerulosclerosis.
H &E stain, magnification 40x



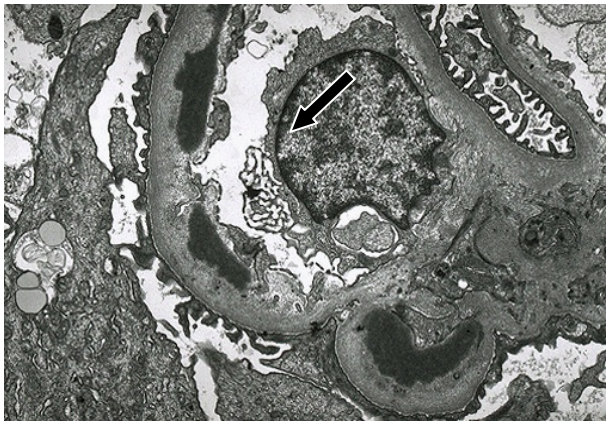
Picture 11 Acute interstitial nephritis.
Arrow points to dense mononuclear cell infiltration.
H &E stain, magnification 10x.



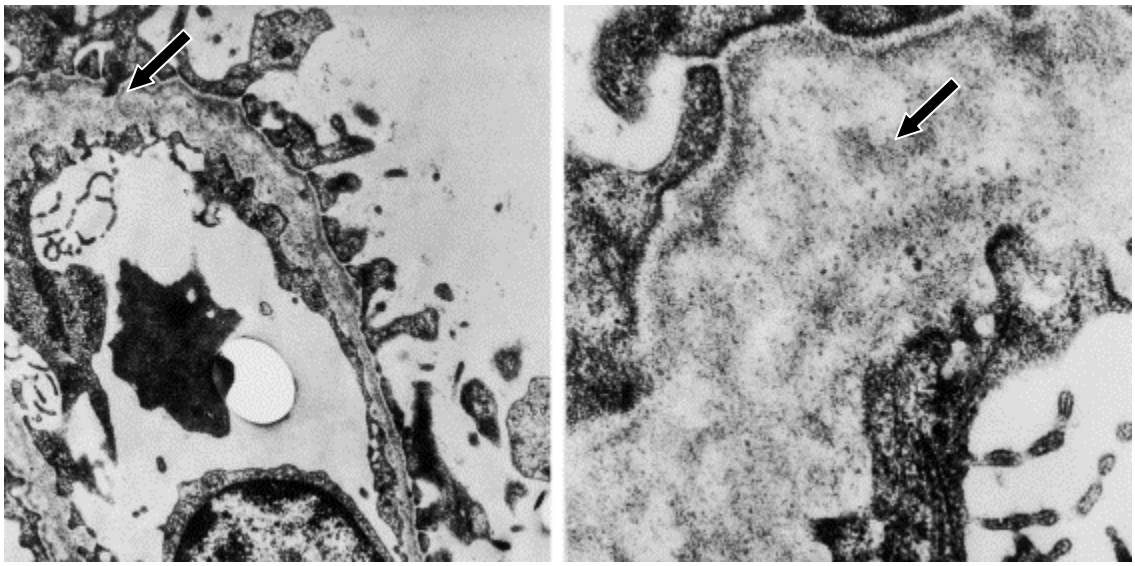
Picture 12 Acute tubular necrosis.
Arrow points to injured tubules,loss of tubular epithelial cell height and brush burder. H &E stain, magnification 40x.



Picture 13 Minimal change disease. Diffuse effacement of foot processes seen on electron microscopy (×800)



Picture 14 MPGN type II Electron dense deposits within the basement membrane electron microscopy (×800)



Picture 15,16 : Alports syndrome . Arrow shows basement membrane showing segments of thickening and thinning with irregular contours (left panel). Magnification of a thickened segment showing lamellation, electron-lucent areas and electron-dense granules (right panel).

PROFORMA

A. Patient Information:

1. Case Number:
2. Name:
3. Hosp_No:
4. Age:
5. Gender : Male - 0 / Female - 1
6. Ht: Cm
7. Wt.: Kg.
8. State Code:

B. Clinical Features:

9. Edema: No- 0 / Limited-1 / Generalised - 2
10. HTN: No - 0 / Yes - 1
11. Hematuria: No - 0 / Microscopic - 1 / Macroscopic - 2
12. Oliguria : No - 0 / Oliguria - 1 / anemia - 2
13. Skin Rash: No - 0 / Yes - 1
14. Eye abn: No - 0 / Yes - 1
15. Hearing : No - 0 / Yes - 1
16. Pallor : No - 0 / Yes - 1
17. Arthritis: No - 0 / Yes - 1
18. Others if any:
19. Duration of Illness (in Weeks) :

C. Lab Investigations :

20. HB:
21. Urea:
22. Creatinine:
23. S.Alb:
24. 24hr U/P :
25. U/P.Ct.Ratio:
26. Ur.Alb:
27. Ur.RBC:

28. Ur.WBC:
29. S.Cholestrol:
30. ANA:
31. DSDNA:
32. Total Comple:
33. C3 :
34. C4:
35. ANCA-C:
36. ANCA-P:
37. ASO:
38. ADNB:
39. RA:
40. HbsAg:
41. HCV Ab:
42. HIV:
43. Croglobulin:

D. **Clinical Syndrome:**

Acute Nephritic Syndrome - 1
Nephrotic Syndrome - 2
ARF - 3
RPRF - 4
Sev.RF unknown etiology - 5
Asymtomatic hematuria - 6
Subnephrotic protein nos - 7
Others - 8.

E. **Biopsy Details:**

45. Biop_Date:
46. Bx_No:
47. Bx.LM:
48. Tot_No of glom:

49. Tot_No of scle:

50. No of glom Crescent:

51. Tubulo.Interstitial / Infiltration: No - 0 / Mild - 1 / Moderate - 2 / Severe - 3

52. Interstitial fibrosis : No- 0 / Focal - 1 / Diffuse – 2

IF:

IgG : No - 0 / 1+ / 2+ / 3

IgA : No - 0 / 1+ / 2+ / 3+

IgM: No - 0 / 1+ / 2+ / 3+

C3 : No - 0 / 1+ / 2+ / 3+

C4: No - 0 / 1+ / 2+ / 3+

Pattern:

Course Granulor - 1
Linear contiguous - 2
Arborising - 3
Non specific - 4

Location:

Mesangium - 1
Capillay Wall - 2
Sclerotic tufts - 3

Complications:

No - 0
Bleeding - 1
Infections - 2

EM :

Treatment:

Rx. given : No - 0 / Yes - 1

What Rx : **Sterioid -** No - 0 / Yes - 1

Endoxen : No - 0 / Yes - 1 / Oral / IV

CSA : No - 0 / Yes - 1

Tacro: No - 0 / Yes - 1

Aza: No - 0 / Yes - 1

ACEi: No - 0 / Yes - 1

ARB: No - 0 / Yes - 1

Keto: No - 0 / Yes - 1

Levamisole: No - 0 / Yes - 1

MPA : No - 0 / MMF - 1 / MM Na - 2

Follow - Up: No - 0 / Yes - 1

Lab Investigations:

Investigations	**Visit 1**	**Visit2**	**Visit3**	**Visit4**	
Date of visit					
Symptoms					
Height					
Weight					
S.Creatinine					
S.Urea					
S.Alb					
24hr U/P					
U/P creat ratio					
HB					
S.Chol					
Remission					
Change of Rx					
Drugs with levels					
Change of protocol					
Duration of Rx					
Symptoms: Worse - 0 Same - 1 Improvement - 2 No Sym. - 4					
Last Visit Date					

Note.:**For Drugs** if CSA - CO, C2 / Tac-CO / MPA - AUC